JUN 22 1931

INDEX NUMBER

VOLUME 4 JUNE, 1931 NUMBER 12
(Old Series, Vol. IX)

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

CONTENTS

	PAGE
The Electrocardiogram in Angina Pectoris. MORRIS H. KAHN	1499
The Relationship of Pain to Jaundice. JAMES F. WEIR and WALLACE T. PARTCH	1509
Appendiceal Oxyuriasis. HAROLD GORDON	1521
Idiopathic Thrombopenic Purpura. ERASTUS I. GULLER and JOHN S. LAWRENCE	1535
Chronic Mercurial Poisoning Simulating Acute Cholecystitis and Choledocholithiasis. J. W. HINTON	1545
The Diagnosis of Pre-Clinical Tubercle in Suspects and Contacts by Caulfeild's Inhibitive and the T. C. F. Part II: Clinical Application. WILLIAM E. OGDEN	1551
Some Observations as to the Results of Phrenic-Exeresis in Pulmonary Tuberculosis. A. T. COOPER	1569
Primary Tuberculosis of the Spleen. ALVIN E. PRICE and RONALD L. JARDINE	1574
Superior Longitudinal Sinus Thrombosis With Subarachnoid Hemorrhage. ROY S. LEADINGHAM	1584
Gland Extracts in Experimental Carcinoma and Sarcoma of Albino Rats. O. M. GRUHZIT	1589
Amebic Dysentery: Sugar Cane as a Possible Distribution Hazard. MILLS STURTEVANT	1598
Reasons for the Artist's Conception of the Physician. BEN WOLEPOR	1601
Editorials	1608
Abstracts	1612
Reviews	1614
College News Notes	1616
Index	1631

Issued Monthly
ANN ARBOR, MICHIGAN

ANNOUNCING A HISTORICAL STUDY OF THE EVOLUTION OF THE DANCE OF DEATH MYTHUS IN ART, THROUGHOUT SIX CENTURIES.

LIMITED EDITION
[1000 NUMBERED COPIES]

THE PHYSICIAN OF THE DANCE OF DEATH

By

ALDRED SCOTT WARTHIN

PH.D., M.D., LL.D.

Professor of Pathology & Director of the Pathological Laboratories in the University of Michigan, Ann Arbor

THIS study of man's changing psychical reactions to the concept of Death, throughout six centuries, has occupied the author in his leisure hours ever since, as a young medical student on his way to Vienna in 1893, his interest was aroused in a print which he saw in a shop window in Nuremberg. It was Albrecht Durer's "Ritter, Tod und Teufel." Eventually, three prints formed the beginning of a collection of the representations of Death in Art, that grew into the collection of the Dance of Death, about which this book has been written.

The author's usual interesting style of presentation is augmented by ninety-two illustrations depicting the various concepts of Death throughout six centuries.

SPECIAL LIMITED EDITION—ONE THOUSAND NUMBERED COPIES.
QUARTO, 158 PAGES, 92 ILLUSTRATIONS - - - - - - $7.50 net

FIRST HUNDRED COPIES AUTOGRAPHED, BOUND IN FABRIANO PAPER SIDES, LINEN BACK, WITH SLIP CASE - - - - - - - $12.50 net

Complete Catalogue and Circulars on Request

PAUL B · HOEBER · INC · PUBLISHERS

SEVENTY-SIX FIFTH AVENUE · NEW YORK, N.Y.

Publishers of *Annals of Medical History; The American Journal of Surgery; Annals of Roentgenology; Clio Medica*, etc.

The Electrocardiogram in Angina Pectoris

By Morris H. Kahn, M.A., M.D., *New York City*

An abundance of literature is devoted to the syndrome of angina pectoris. And yet, after two decades of the intensive use of the electrocardiograph in diagnosis in these cases, no general opinion has been reached as to the pathologic changes that underlie this distressing disease. The reason for this is to be found in the fact that angina pectoris is not a pathological entity. It is rather the clinical manifestation of disease processes in the heart muscle, in the coronary arteries or in the aorta, producing pain of more or less typical character. We must accept the possibility of different lesions in different cases. On this account we cannot *a priori* expect unfailing assistance from the electrocardiogram either in the diagnosis of these cases or in the prognosis.

In his book on this subject, Sir James Mackenzie knowingly omits all discussion of the electrocardiograms of his cases, each of which he so carefully reviews from a clinical diagnostic standpoint. Sir Clifford Allbutt comes to the conclusion that the electrocardiogram cannot reveal intrinsic functional values in the heart's capacity, but he does not discuss its diagnostic value in angina pectoris. Harlow Brooks, in an excellent monograph on the subject, emphasizes that the negativity of electrocardiographic findings does not exclude angina. He states, on the contrary, that "any electrocardiographic finding which indicates, in so far as the electrocardiogram may, disease of the heart muscle or of the coronary vessels is to be considered as highly confirmatory evidence when the clinical aspects of the case suggest angina. Serious consideration should be given to positive cardiographic findings even in the absence of clinical evidence, if these findings are of sufficiently definite and constant character. Negative findings are to be considered clinically as merely negative findings, and much clinical weight must not be attached to them."

We have been led to the same conclusion as a result of the analysis of the electrocardiograms of our series of three hundred and thirty cases of clinical angina pectoris which have been under our observation for a number of years. In this paper we shall present the data, correlating them with other and interesting clinical features.

Classification

The classification of electrocardiograms into particular groups presents considerable difficulty. First, the multiple waves, P, R, T, in the electrocardiogram, may all show simultaneous abnormalities, which, in the combination, will not permit grouping with

other records. Thus the P wave, the P-R interval, the QRS wave, the S-T phase, the T wave and the intercyclic period may each or all present notable variations from the normal. It would be almost impossible to classify electrocardiograms if every detailed alteration from the normal were given equal weight. Secondly, electrocardiograms naturally alter with the advent of time and the concomitant effects of senescence and with the development of pathological processes in the heart. Progressive changes are all the more likely in individuals in whom disease has already produced severe clinical symptoms. Therefore, repeated films, taken at intervals of months or years, often show remarkable differences one from the other. Such cases would therefore require classification into several different groups. Finally, the electrocardiographic features themselves, even if definite and more or less constant, often have equivocal significance, leaving us uncertain as to whether the condition is functional or pathologic.

We at first tabulated the electrocardiograms according to the individual features present, listing those showing left ventricular preponderance, right ventricular preponderance, P2 wave widened, QRS wave widened, T1 inverted, T3 inverted, low voltage, bradycardia, and so forth, but we found that such a classification was unwieldy and was entirely unrelated to the clinical picture of the various cases.

In consequence of the above considerations we therefore classified the electrocardiograms in a more composite way. We recorded the one or two most notable electrocardiographic features in each case. The electrocardiogram was negative in 54 cases, or 16% of the series, in which cases it showed no significant abnormality. Left ventricular preponderance, which must be considered a negative feature in diagnosis, was noted in 83 otherwise negative records, or 25%. Right ventricular preponderance, on the other hand, occurred in only two cases. The T wave was inverted in Lead 1 in 39 cases, or 12%, and it was inverted in Lead 3 in 102 cases, or 31%. A typical so-called Coronary T wave was observed in only 12 cases, or 3.6%. The QRS wave was widened in 20 cases, or 6%, and the S-T phase was strikingly abnormal as an only feature in one case. Low voltage was the sole feature in 10 cases, or 3%. Bundle branch lesions were present in 7 cases, or 2%. The table shows these proportions at a glance.

We want at this time to point out that over 40% of the three hundred and thirty cases of clinical angina pectoris showed electrocardiograms that were essentially negative as far as the diagnosis of the disease is concerned. Over 30% of the series showed inversion of the T wave in Lead 1.

Coronary closure as diagnosed from the electrocardiogram, with the conspicuously abnormal T wave and convexity of the S-T phase, was observed in only a small number of the cases, 12, but the history in a larger number indicated the previous occurrence of an attack of stenocardia. The electrocardiographic effects of acute coronary closure are not uniform nor permanent, because they naturally vary with the location of the involved vessel and its

TABLE OF ELECTROCARDIOGRAPHIC FINDINGS IN ANGINA PECTORIS

EKG Findings	No. of Cases	% of Cases	No. Died	% Died
Negative	54	16	5	9
plus Left Ventr. Prepon.	77	23	1	1.3
plus extrasystoles	5	1.5	2	40
plus Auric. Fibrillation	1	0.3	0	
Total Negative	137	41	8	6
Right Ventricular Preponder.	1	0.3	0	
plus Auric. Flutter	1	0.3	0	
Total Right Ventr. Prep.	2	0.6	0	
T-1 Inverted	10	3	3	30
plus L. V. P.	29	9	1	3
Total T-1 Inverted	39	12	4	10
T-3 Inverted	31	10	2	6
plus L. V. P.	71	21.5	1	1
Total T-3 Inverted	102	31	3	3
Coronary T Wave Observed	12	3.6	3	25
Q R S Widened	20	6	5	25
S-T Phase Abnormal	1	0.4	0	
Low Voltage	10	3	1	10
Bundle Branch Lesions	7	2	4	57
Total Number Of Cases	330		23	7.

size, and with the pathologic changes that take place after the thrombosis has occurred.

MORTALITY PROGNOSIS

Of our series of three hundred and thirty cases of angina pectoris, 23, or 7% died suddenly or in the course of an attack, or from acute coronary closure. Of course, the presence of bundle branch lesions, indicating widespread myocardial changes, seriously affected the prognosis. Four of the seven cases showing this pathology died. Of the group of cases showing a Coronary T wave, 25% proved fatal. The same percentage mortality was found among the group showing widening of the Q R S wave. Of the cases with inverted T in Lead 1, 10% were fatal, and of those with inverted T in Lead 3, only 3% died.

REPORT OF CASES

As is to be seen from the Table, eight of the fatal cases, or 30% of them, had negative or insignificant electrocardiograms during the entire time of our supervision, while they were suffering from repeated or severe attacks. It is these cases especially that we want to record, to emphasize our belief that the electrocardiogram cannot play a crucial or decisive part in the diagnosis or in the prognosis of angina pectoris. At the same time we shall report illustrative cases from the various groups listed in the Table to show by contrast the informative value of the electrocardiogram when exten-

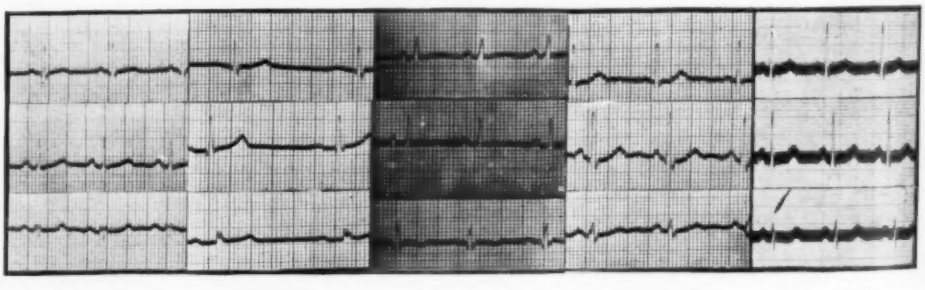
sive myocardial disease is present. It must be remembered that in angina pectoris this is usually absent.

FATAL CASES WITH EKG NEGATIVE

Case 1: Mrs. I. L. B., aged 50, had for two years sudden attacks of dizziness and for some weeks dyspnea and palpitation and fatigue on exertion. Precordial pain was felt under the left breast. The heart showed an atheromatous systolic blow over the apex and the aortic area, and the blood pressure was 198 over 110 mm of mercury. Three years later the precordial pain was more severe and there were attacks of severe pressing sensation across the sternum, the pain radiating to the left shoulder, with pallor, weakness and dyspnea. The heart rate was 120 despite the adequate doses of digitalis that were given, extrasystoles were frequent, the heart percussed enlarged to the right and left, and the apex beat was forceful out of proportion to the faintly audible first sound. Clinically the diagnosis of angina pectoris was made and aneurysm of the left ventricle was suspected to exist. *The electrocardiogram was negative.* The attacks of precordial distress and marked oppression in the chest became more severe, and in a short time sudden death occurred.

Case 2: Mr. Meyer B., aged 51 years, had felt dyspnea on exertion for six years. For eight months he felt a pressing sensation after exertion across the upper sternum and upper precordial region, the pain at times radiating into the left shoulder, both upper arms and the back of the chest. These attacks were at times quite severe, and the patient was always compelled by the feeling of constriction across the chest to stop after walking two city blocks. The attacks were relieved by the inhalation of amyl nitrite. The heart showed a faint systolic aortic murmur, and frequently a tender spot high up in the left axilla; the blood pressure varied during the three years of observation between 146 over 88 and 176 over 100. *The patient was seen often, electrocardiograms were taken repeatedly, and they were always essentially negative.* The day after he was last seen, after walking up some stairs the patient had a severe attack of angina pectoris with coronary closure and cyanosis and died. *The electrocardiogram from this case is reproduced in Figure* 1.

Case 3: Alexander H., a painter, aged 47 years, gave a history of untreated syphilis at the age of 22. For two years he had dull sternal pain and a feeling of oppression on exertion and after excitement which sometimes radiated to the left precordial region and into the left elbow-joint. Such attacks latterly occurred after walking half a block with palpitation and dyspnea. The aortic second sound was sharply accentuated, and there was audible a blowing systolic aortic murmur. The blood pressure was 130 over 55. The patient was seen in an anginal attack, in which while dressing he had to remain standing quietly for five minutes with pain over the manubrium. *The electrocardiogram showed no abnormalities.* Subsequently during a severer attack of angina pectoris the patient died suddenly.



DAVID H. A. LOUIS M. MICHAEL S. MEYER B. ISRAEL L.

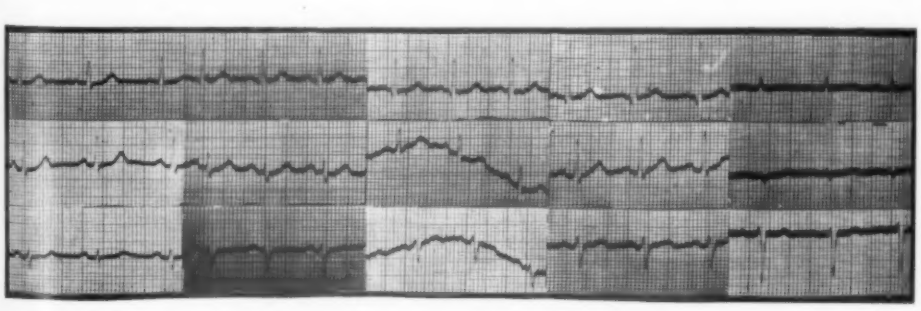
FIG. 1. Electrocardiograms from the group of cases of angina pectoris which showed negative electrocardiograms.

Case 4: Israel L., aged 52 years, complained of pain across the front of the chest for several years with attacks of palpitation and a feeling of oppression behind the sternum, the pain lasting five to fifteen minutes radiating to the left upper arm and back, with a feeling of mortal anguish. *The electrocardiogram was negative* and yet the patient died suddenly shortly after in a typical attack of angina pectoris. (Figure 1).

Case 5: Mr. Louis M., a farmer, 67 years old, developed attacks of precordial pain, with a distressing burning sensation across the sternum which developed even after mild exertion several times daily, together with a feeling of weakness, severe pallor and profuse perspiration. The heart beat was felt very faintly, the sounds were poor and inaudible at the base, but there was roughening of the systolic sound at the apex. There were tender spots in the precordial area. *The electrocardiogram was negative but for a rare extrasystole and sinus bradycardia* (See Figure 1). The blood pressure was 112 over 70 mm. of mercury. Eight months after the patient came under our observation, *repeatedly showing negative electrocardiograms,* he died suddenly, in a severe attack of angina pectoris.

Case 6: Mr. Sol M., aged 47 years, had several attacks of "acute indigestion" four years before he came under our observation, in which the sudden pain radiated up to the throat. Six months before his first visit, he had such a sudden attack, with pain in the upper dorsal region, radiating into both arms, and on attempting to move the pain became terribly severe in the lower sternal region, with extreme pallor and cold sweat, and dyspnea, and morphine was ineffectual to relieve it. Gradually the pain radiated to the left upper pectoral region, which became very tender to touch, and the patient had to stay for three weeks abed before he felt improved. Since then, after walking a block, pain returned in the mid-dorsal spine with weakness and dyspnea which were relieved by rest. Several attacks of vise-like pain in the precordium recurred with a sensation of clutching in the right side of the throat and pain in the right lower face. The heart apex was visibly forceful, but on auscultation the first sound was contrastingly weak, with audible systolic gallop rhythm. The *radial pulse showed distinct pulsus alternans, but the electrocardiogram showed only left ventricular preponderance.* The blood pressure was 150 and 146 over 94 mm. of mercury, the liver was enlarged, and a diagnosis of angina pectoris was made with aneurysm of the left ventricle. Despite extreme care and absolute rest, the patient died shortly after in an attack.

Case 7: Mr. Melville J. S., a retired banker, aged 57 years, complained for two and a half years of a burning distressing feeling across his chest which came on while walking or climbing stairs, with some dyspnea and occasional feeling of faintness and palpitation. The blood pressure was 140 over 90, but the heart sounds seemed fair in



LOUIS P. JULIUS P. GUSSIE S. MAX B. JOSEPH W.

FIG. 2. Electrocardiograms from the group of cases of angina pectoris which showed only left ventricular preponderance.

quality. *The electrocardiagram showed only left ventricular preponderance,* on repeated examinations over a period of two years. The patient then died suddenly with an attack of angina pectoris.

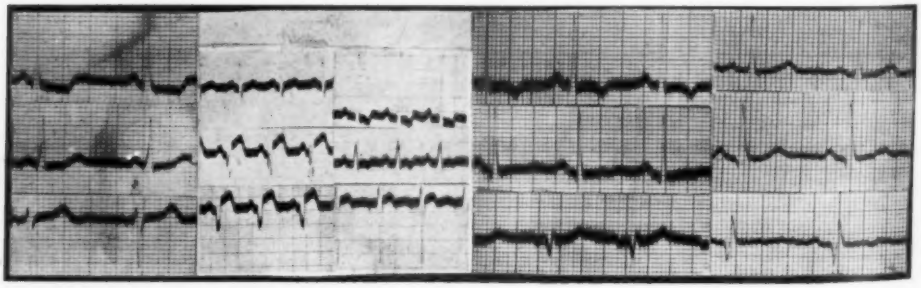
FATAL CASES WITH T INVERTED IN LEAD I.

Case 1: Mrs. Fanny W., aged 60 years, developed pressing pain in the middle of the chest, and suddenly had a severe attack which compelled her to lie down with palpitation, pallor, dyspnea, and an agonizing feeling of anxiety as if she were dying. The pain radiated directly to the spine, and was relieved by morphine only after three hours. Milder attacks and an occasional severe attack occurred, and the patient gradually developed dyspnea and palpitation on exertion. The heart was enlarged toward the left and its sounds were of poor muscular quality. The blood pressure was 158 over 88. The condition lasted under our observation for a period of seven years after which the patient died. *The electrocardiogram showed only left ventricular preponderance and partial inversion of the T wave in Lead* 1; *it was otherwise negative.* (See Figure 3).

Case 2: Mr. Max B., a tailor, aged 48 years, had a sudden pressing sensation in the midsternal region, with a numb drawing sensation across the chest and down the middle of both arms to the front of the wrists. He had profuse cold sweat and pallor with it, and the attack lasted twelve hours. Following that attack he had continuous precordial pain and frequent less severe attacks. The heart was slightly enlarged, the sounds were of poor quality, and there was a systolic blowing murmur at the apex. The blood pressure was 120 over 112, and the peripheral vessels were somewhat tortuous. *The electrocardiogram showed inversion of the T wave in Lead* 1. The patient died of myocardial failure after two years of observation.

Case 3: Harry I., a chauffeur who had a positive blood Wassermann test, at the age of 49 years, was taken with sudden sharp severe pressing pain in the middle of the lower sternal region, with pallor and cold sweat. The attack lasted three hours. Such attacks recurred often at night, waking the patient, always with pallor and cold sweat. The pain radiated through to the back and down both arms to the elbows. After walking a block he had to stop because of pain and later also dyspnea and palpitation. The heart was very much enlarged with double aortic murmur and peripheral vessel tortuosity. The patient died with cardiac asthma and anginal pain. *The electrocardiogram showed inversion of the T wave in all three leads, more in Lead* 1 *than in Lead* 3. This case may be grouped with the cases showing Coronary T. (See Figure 5).

Case 4: Perez B., aged 54 years, developed burning pain behind the sternum, which soon became constant and radiated to the precordial region and to the middle of the back. He was seen in an attack of dyspnea, cyanosis of the lips, complaining of pain in the epigastrium and in the precordial regions. *One electrocardiogram*



FANNY W. PEREZ B. MR. I. L. P. JOSEPH H.

FIG. 3. Electrocardiograms from the group of cases of angina pectoris which showed T inversion in Lead 1.

showed only left ventricular preponderance. A few days later it showed marked QRS notching in Leads 2 and 3, and the foot points of QRS were separated. The T wave was continuous from R. (*See Figure 3*). Four days later the patient became restless, with anxious face, dyspnea, severe substernal distressing pain and profuse perspiration. Twenty minutes later the breathing became very difficult, râles filled the chest, extrasystoles developed with a heart rate of only 70, and death took place with pulmonary edema.

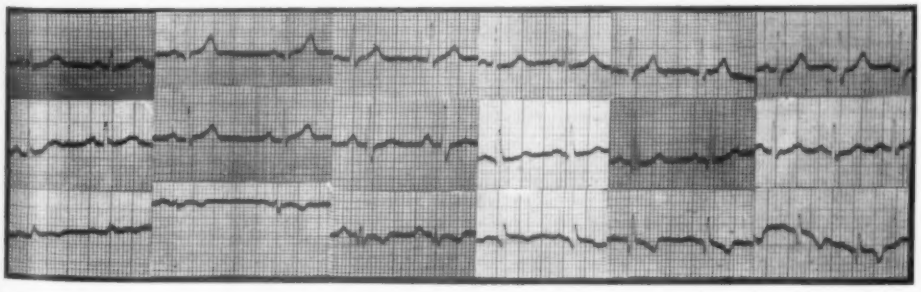
Case 5: Mr. I. L. P., a retired banker, aged 51 years, had several severe attacks of angina pectoris, which occurred regularly after walking one or two blocks even on level ground. *The electrocardiogram showed only inversion of T in Lead 1.* In a severe attack of coronary closure, after a few years of observation, the patient died. (See Figure 3).

FATAL CASES WITH T INVERTED IN LEAD 3.

Case 1: Joseph H., at the age of 57 years had a sudden attack of burning pain over the sternum radiating down the left arm to the fingers and compelling the patient to rest standing for five minutes. After that he had a burning sensation across the chest after exertion. A severe attack, with a feeling of imminent death, extreme pallor and cold sweat occurred a year later, with constricting pain in the upper abdomen radiating up to the front of the chest, and a severe burning sensation radiating down the left arm and hand. At that time he became cyanosed and almost pulseless. Moderately severe and milder attacks recurred, often with cyanosis, pallor and cold sweat and a feeling as if he were dying. The heart was not enlarged, the sounds were of fair quality, and the blood pressure was 150 over 90 mm. of mercury. After five years of such attacks *the electrocardiogram showed only slight inversion of T in Lead 3.* Several severe attacks occurred within a month while the patient was kept at absolute rest, and the patient died. (See Figure 3).

Case 2: Dr. George A. M., began to have anginal pain across the chest with simultaneous pain in both forearms when he was 56 years old. After eight years of this disease, the heart sounds were poor in quality, the heart was not enlarged, and the blood pressure was 146 over 80 mm. of mercury. *The electrocardiogram showed the T wave inverted in Lead 3*, but no other abnormality. Within a month after the last electrocardiogram, without premonitory symptoms, the patient died suddenly while seated in a train.

Case 3: Michael S., a jeweler 43 years old developed after exertion a sudden jamming pain across the front of the chest, which was relieved after resting for one hour. It recurred as a feeling of a lump at the upper sternum and again as an attack of epigastric pressing during the night with dyspnea and a burning sternal sensation. The heart and aorta percussed enlarged with poor first sound, and a blood pressure of 144 over 88. *The electrocardiogram showed only slight*



PHILLIP L. JACOB G. JACOB G. SHEVE R. MAX N. ANNIE V.

FIG. 4. Electrocardiograms from the group of cases of angina pectoris which showed T inversion in Lead 3.

inversion of T in Lead 3. After one year of observation he was feeling better but like the previous case, he was found dead in a Pullman train on his way home from a business journey. (See Figure 1).

FATAL CASES IN WHOM CORONARY T WAVE WAS OBSERVED

Case 1: Hyman B., a presser 46 years old, had almost daily attacks of epigastric and substernal pressing and sticking pain which compelled him to rest after walking one block. He had dyspnea and palpitation even at rest with a feeling of weakness in the left arm. The aorta was slightly widened and there was a faint systolic murmur at the apex. The brachials and temporal arteries were palpably tortuous, and the blood pressure was 198 over 88. *The electrocardiogram showed only left ventricular preponderance.* Seven months later after a severe attack of sudden gnawing and aching pain in the midsternal region which radiated to both shoulders and into the right wrist and lasted all night, *the electrocardiogram showed a striking abnormality in the T wave in Leads 2 and 3. The T wave is pronouncedly and sharply inverted in these Leads.* After another year and a half of recurring milder attacks *the electrocardiogram showed only slight inversion of the T wave in Lead 3,* and six months later the patient died. (See Figure 5).

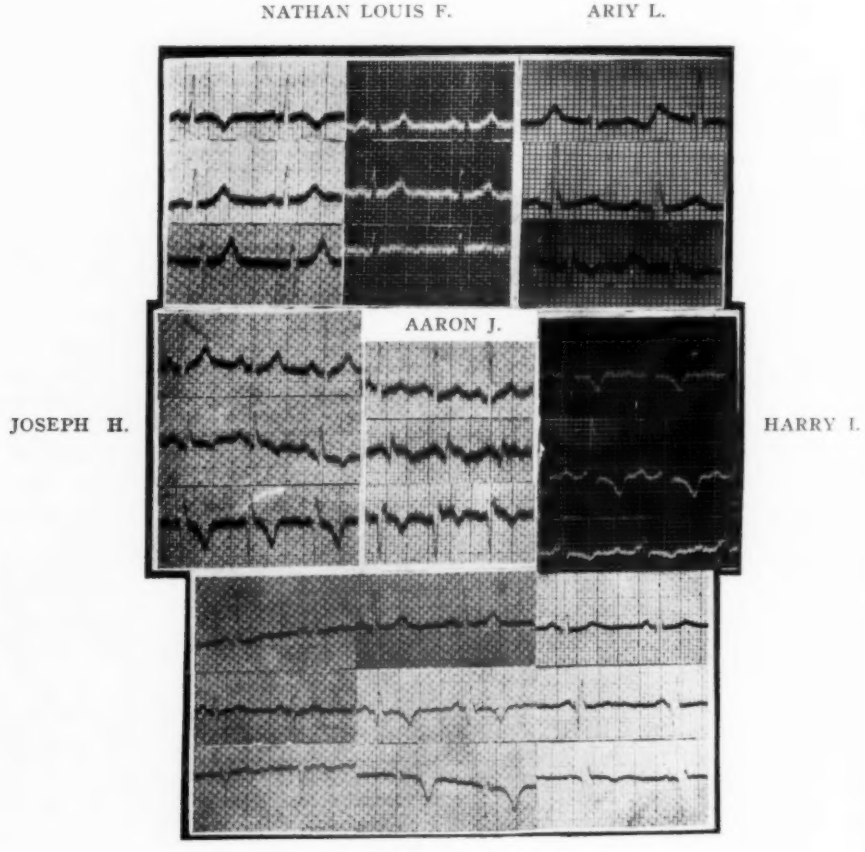


FIG. 5. Electrocardiograms from the group of cases of angina pectoris which showed coronary T wave changes after a severe attack.

Case 2: Ariy L., 61 years old, had for fifteen years frequent burning sensation over the lower sternum, and dyspnea on exertion. On July 6, 1926, a sudden sharp burning sensation shot across the precordium to the middle of the left arm. He also felt a constricting pain across the chest which was relieved after an hour by morphine and nitroglycerine. Similar milder attacks recurred after walking upgrade. Except for a tender spot over the aortic region the heart examination was negative. The blood pressure was 136 over 88. *The electrocardiogram showed left ventricular preponderance and a Coronary T wave in Leads 2 and 3.* (See Figure 5).

Case 3: Mr. Nathan Louis F., aged 54 years, had a sudden attack of severe sticking pain in the middle of the chest, radiating to the left arm. Physical examination showed a sallow pallor, but otherwise the heart examination was negative. *The electrocardiogram showed left ventricular preponderance and complete inversion of the T wave in Lead 1.* This was interpreted as the coronary form of T wave, and the diagnosis of angina pectoris was made. For four years the patient continued in fair health, complaining of only occasional pressing sensation across the sternum which was relieved by nitroglycerine. *His electrocardiogram became normal.* He then began to have severe attacks of typical angina, which continue to occur frequently at the present writing. (See Figure 5).

Case 4: Mr. Joseph H., 44 years old, while walking, had a sudden cramp-like sensation in the front of the left shoulder shooting down the arm, with cold perspiration. He ran into a hallway and rested, but that night the attack recurred and lasted all night. From that time on he had pain on walking which frequently radiated to the little finger of the left hand, and once he fainted in such an attack. The examination showed the presence of diabetes and moderate arteriosclerosis, and *the electrocardiogram showed a marked Coronary T wave.* (See Figure 5).

Case 5: Aaron J., a tailor sixty-five years old, had his first severe attack of anginal pain on walking up two flights of stairs. The pain across the chest radiated toward the left shoulder, and was associated with dyspnea and palpitation. He had dyspnea and nocturnal asthma. The heart was enlarged to the left and there was a palpable thrill over the apex and aortic region with a rumbling systolic murmur. *The electrocardiogram showed left ventricular preponderance, the T wave inverted in Leads 2 and 3, with abnormality of the S-T phase.* (See Figure 5). The heart showed occasional extrasystoles and periods of auricular flutter which subsided under the use of quinidine. The patient remained in bed with progressive myocardial failure and died suddenly.

Comments and Conclusions

We deemed it desirable for the sake of emphasis and for purposes of critical presentation to outline the main features of the cases that are here recorded and to reproduce the illustrative electrocardiograms, in order that the reader may perceive at a glance the relative unimportance of the electrocardiogram in the clinical diagnosis of angina pectoris.

We may therefore conclude this paper with the following general assertions:

1: The diagnosis of angina pectoris rests on the clinical features, particularly on the symptomatic attacks.

2: In cases of clinical angina pectoris any abnormality of the electrocardiogram, however trivial, may be significant.

3: The alteration in form of the T wave following a minor attack is a gradual one, except where there is massive occlusion, so that every alteration is important.

4: In order that the electrocardiogram should serve best in diagnosis

frequent records should be made at intervals.

5: A series of three hundred and thirty cases of typical angina pectoris is analyzed, of which twenty-three or seven per cent died during an attack.

6: Of all the cases, one hundred and thirty-seven, or forty-one per cent showed negative electrocardiograms during the entire period of observation.

7: Of the fatal cases, thirty per cent had negative or insignificant electrocardiograms during the entire time of our supervision.

8: In the evaluation of the electrocardiogram as an aid in the diagnosis of angina pectoris, it must be remembered that negative findings must be dismissed from consideration while even trivial findings may have weighty significance in diagnosis.

The Relationship of Pain to Jaundice*

JAMES F. WEIR, M.D., *Division of Medicine, The Mayo Clinic, Rochester, Minnesota,*
and
WALLACE T. PARTCH**, M.D., *Welborn Hospital Clinic, Evansville, Indiana*

IN THE last decade certain adjustments have been made in our conception of jaundice. This has been due largely to the application by van den Bergh of Ehrlich's diazo reagent to the blood serum and to the demonstration by Mann and his associates, and others, that bilirubin forms chiefly outside the liver and that the polygonal hepatic cell is the normal pathway of excretion of bilirubin. Jaundice may be produced in one of three ways: obstruction of the biliary passages, increased production of bilirubin beyond the ability of the liver to excrete it, or functional derangement of the polygonal hepatic cell interfering with the excretion of the pigment. On this basis, McNee proposed that jaundice be classified into three clinical types: obstructive, hemolytic, and toxic or infectious. We have found this a practical classification.

Numerous pathologic processes lead to the development of jaundice, and one is often impressed with the extreme difficulty frequently encountered in making a satisfactory clinical diagnosis. Many factors in the clinical history, the physical condition, or laboratory data enter into this evaluation. McVicar and Fitts suggested that the essentials of a workable procedure include: (1) the character of the van den Bergh reaction; (2) the height and behavior of the serum pigment curve; (3) the quantity of bile reaching the intestines as determined by siphonage of the duodenal contents, and (4) the presence or absence of pain and its character. The clinician's first duty in such cases is to separate them into surgical and nonsurgical groups; we believe that pain is one of the most significant single factors in such differentiation.

TYPES OF PAIN

We are presenting a review of 275 consecutive cases of jaundice recorded in The Mayo Clinic between 1926 and 1928 inclusive with regard to the frequency of occurrence, general character, duration and site of pain, and the relationship of pain to the onset of icterus. It is important to ascertain the time relationship of the pain with respect to the onset of jaundice; if pain occurred within one month of the

*Submitted for publication February 11, 1931.

**Work done while a Fellow in Medicine, The Mayo Foundation, Rochester, Minnesota.

recognition of the jaundice we arbitrarily assumed the possibility of relationship. Although there are exceptions to every generalization, as will be shown, pain associated with jaundice is usually indicative of obstruction of the biliary tract. A summary of the data is given in tables 1 and 2. Various types of pain are encountered: (1) typical colic; (2) colic atypical as to character or site; (3) pain of a dyspeptic nature, gaseous or ulcer-like; (4) constant or boring pain, and (5) miscellaneous associated pain.

Typical colic.—The so-called biliary colic is the most common type. In its typical form it is characterized by sudden, severe pain in the epigastrium or right upper part of the abdomen, often requiring opiates for relief, and often radiating to the right subscapular region. Associated symptoms include diaphragmatic spasm interfering with free respiration, gastric disorders such as belching, nausea, and vomiting, and various degrees of shock manifested by weakness, perspiration, pallor, acceleration of pulse, and prostration. The pain may cease suddenly, often leaving tenderness.

There is no satisfactory explanation of the mechanism of the colicky pain in disease of the biliary tract. This was considered by Graham and his associates, who stated: "In the absence of any positive evidence one is forced to conclude that the origin of the pain cannot be satisfactorily explained at the present time."

Typical colic in definite association with jaundice was present in 136 cases of this series. One hundred seventy-

TABLE 1

275 Consecutive Cases of Jaundice

Major Pathologic Condition	Cases	Colic		Atypical Pain		Painless onset	Pain later
		Recent	Previous	Recent	Previous		
Stones in common duct (no previous operation)	59	45	49	9	17	9	2
Stones in common duct (previous operation)	45	35	40			10	
Total	104	80	89	9	17	19	2
Benign stricture of common duct	49	22	41	8		27	
Malignant lesions							
Ducts, ampulla, and duodenum	9	1		1	1	7	
Head of pancreas	38	5	8	13	6	19	2
Gallbladder with extension to ducts	5	1	2			3	2
Liver (metastatic)	7	1	3	2		3	2
Total	108	30	54	24	7	59	6
Chronic cholecystitis with stones	25	14	17	3	2	8	4
Miscellaneous: cholangeitis, biliary cirrhosis, "intrahepatic," indeterminate	38	12	16	5	7	21	1
Total	63	26	33	8	9	29	5
Total	275	136	176	41	33	107	13

six patients gave a history of colic at some time during the course of their illness. Colic occurred most frequently in conditions associated with calculi, cholangeitis, and strictures. However, it occurred in enlargements of the head of the pancreas quite frequently; occasionally, in cases of apparent primary hepatic disease there is sufficient pain to cause difficulty in arriving at an accurate clinical diagnosis.

Atypical colic.—Atypical colic both as to character and situation may vary from acute attacks of more or less severe epigastric discomfort, distention, nausea, and vomiting to mild attacks of gaseous indigestion occurring after large meals. The chief characteristics are the intermittent nature of the spells and the site of pain in the upper part of the abdomen. They may be followed by scleral or generalized jaundice, or the urine may be dark and smoky, and the stools light colored. If there is infection in the biliary tract, fever, chills, and leukocytosis will be present. Such inflammation is nearly always associated with calculi, and if these produce objective signs, the nature of the disease in the upper part of the abdomen may be identified. Individual variation in the recognition of threshold pain in

TABLE 2

CASES WITH PREVIOUS OPERATIONS ON BILIARY TRACT

	Benign stricture of the common bile duct	Stone in the common bile duct
Preoperative (original operation)		
Attacks of colic	41	40
Jaundice	21	27
Postoperative		
Attacks of colic	22	35
Relatively painless onset of jaundice	27	10
Atypical pain	8	
Original operation		
Cholecystectomy	40	21
Cholecystostomy*	9	24
Choledochostomy	6	28
Jaundice or biliary fistula**		
Immediately	35	24
Later (number and average time)	16 7.5 mo.	21 3.67 yr.
No colic at any time	7	2
Total	49	45

*Several patients had had multiple operations.

**Cases are included in this group in which closure of a biliary fistula was followed by jaundice.

various cases may partially explain this situation.

In a few cases the colicky pain was always noted at the left costal margin or in the epigastrium with constant radiation to the left, even as far as the left scapula. There were six cases of this type, but the left-sided colic, of itself, did not indicate the type of disease present.

Pain of a dyspeptic nature.—A varying degree of indigestion may be present with a history of colic, either typical or atypical. This may be periodic or constant and for purposes of discussion will be classified as gaseous or ulcerous in type. The gaseous type is as a rule that usually associated with uncomplicated cholecystitis.

A certain number of the patients complained of an ulcer type of dyspepsia; the number is surprisingly small, however, in contrast to the view sometimes expressed that there is an association between cholecystitis and ulcer, and to Bollman's experiments on animals in which he showed that in a high percentage of dogs with obstruction of the common bile duct acute ulcers developed. Such ulcers are relatively chronic. In nine of the group of cases in which operations had not been done on the biliary tract, the clinical diagnosis of associated ulcer was suggested, in each of which roentgenographic evidence was positive. In five of these cases the lesion was demonstrated at operation; in one case, the patient continued to have symptoms of ulcer after operation, although the jaundice was relieved by the removal of the stone from the common bile duct. In one case, the diagnosis was made by the roentgenogram alone and was not confirmed by operation; in one case the surgeon noted slight edema about the duodenum, but true ulcer could not be demonstrated, and in one in the head of the pancreas with a crater adherent to the duodenum; this case is the only one in the series in which the jaundice may have been due to peptic ulcer obstructing the common bile duct. A few cases presented rather atypical but somewhat suggestive histories of ulcer, but in the absence of laboratory confirmation, the diagnosis was not made, and the surgeon did not find gastric or duodenal lesion at operation.

In twenty-six postmortem examinations of subjects with obstructive benign lesions of the biliary tract, only two had chronic peptic ulcer (both duodenal), neither of which was related to the jaundice. Two other subjects had had acute ulcers. In seventeen postmortem examinations of subjects with obstructive malignant lesions, only one had peptic (duodenal) ulcer. Although this had nothing to do with the cause of jaundice, it happened to be the direct cause of the patient's death by gastro-intestinal hemorrhage. In two other cases of malignant obstruction ulcers were present which were not peptic but a part of the malignant process. In the twenty-six cases, the histories usually suggested long-standing cholecystic disease. In forty-three postmortem examinations on jaundiced subjects the incidence of peptic ulcer was found to be lower than in such examinations performed as a routine.

Constant or boring pain.—The constant or boring type of pain is most

frequently encountered in malignant conditions, although it is noted in cirrhosis, certain other types of intrahepatic disease, pancreatitis, and cholecystitis with stones. In carcinoma of the pancreas it may be severe, seriously disturbing sleep, and not responding to any method of relief other than by opiates. It is usually progressive, and may be referred to the back. In some instances, jarring aggravated the symptoms considerably and was a major complaint of the patient.

Miscellaneous associated pain.—In a few cases various types of distress occurred in the abdomen associated with exacerbations of disease of the biliary tract. Two instances are recalled in which a definite attack of "mucous colitis" occurred with each exacerbation of cholangeitis following repair of stricture of the common bile duct. Physicians occasionally overlook these associated symptoms.

Painless Jaundice

Jaundice of painless onset frequently presents difficulty in diagnosis. If patients are young, the condition may be considered on a toxic or infectious basis, particularly if it develops during an epidemic. In later years, there may be associated symptoms such as a palpably distended gallbladder, a liver containing hard nodules, or evidences of a malignant lesion elsewhere in the body which aid in clarifying the diagnosis. Evidence of a free flow of bile into the duodenum is of value in diagnosis of many of these cases. If the gallbladder has been removed the later development of painless icterus suggests cicatricial stenosis of the common bile duct. However, in spite of all the information that can be accumulated about these cases there are a certain number in which a satisfactory clinical diagnosis cannot be made and in those cases in which the general condition is satisfactory and in which the icterus does not show a tendency to disappear in a reasonable time the advisability of exploration must always be considered. In some cases, however, pain develops later, and this aids materially in the treatment of the patient.

The onset of jaundice was painless in 107 cases and the jaundice was due chiefly to benign strictures, pancreatic enlargements, malignant lesions of the biliary tract, intrahepatic disease, and a moderate number of calculi in the common bile duct. In a considerable number of malignant cases pain developed later.

Stone in the Common Bile Duct

Colic is the most significant single factor in the history of stone in the common bile duct. From a clinical standpoint, if patients are jaundiced and give a history of colic, gaseous dyspepsia, and qualitative food intolerance, one is reasonably certain in making a diagnosis of stone in the common bile duct. As has been mentioned, colic due to gallstones may occasionally be felt entirely in the left upper quadrant, with radiation, if at all, to the left side of the back, and occasionally other pathologic processes will give a similar syndrome.

We have divided these cases of stone in the common bile duct into those in which operations have been performed on the gallbladder or biliary tract, and

those in which operations have not been performed.

Of the fifty-nine cases of stone in the common bile duct with jaundice in which operation had not been performed, recent colic had occurred in forty-five and remote colic (more than one month previous to jaundice) in forty-nine. In most of the cases many attacks had occurred, usually extending over a period of two to three years; in many of the cases, however, the attacks had existed for a longer period, even as long as thirty years. Atypical pain varied in degree, character, and situation, and was frequently associated with colic; it was the chief discomfort in eight cases. Dull epigastric discomfort or aching in the right upper quadrant occurring intermittently or continuously, at times associated with anorexia, nausea, vomiting, and gaseous discomfort, were the chief types. Occasionally the production of symptoms by jarring or the presence of constant soreness was the chief complaint. In nine of the cases of this group jaundice developed without previous pain. The average age of the patients was sixty-four years; the youngest patient was aged fifty years. One patient had had colic after four months of painless jaundice and then the jaundice began to clear rapidly. In each case the obstruction was due to one or more large stones, the smallest being 1 cm. in diameter and the largest 10 cm. long and 8.5 cm. in circumference. Some of the stones were not actually in the common bile duct, but were lodged in the cystic duct or gallbladder and occluded it by pressure from without. In most cases the condition was diagnosed preoperatively as carcinoma of the pancreas.

In the forty-five cases in which one or more operations had been performed on the biliary tract (table 2), recurrent typical colic had occurred in thirty-five and a definite history of stones having been found at previous operation was given in thirty-seven. In twenty-one cholecystectomy had been performed, in twenty-four cholecystostomy, and in eighteen the common bile duct had been opened. In several cases cholecystostomy had been done on more than one occasion and in some cases cholecystectomy had been preceded by cholecystostomy. The patients had had stormy postoperative courses. Chills and fever were common, as were persisting biliary fistulas; when the fistulas closed pain, usually colicky, chills, fever, and jaundice were present. One or all of these symptoms occurred and promptly disappeared on reëstablishment of the fistula. The onset of jaundice was relatively painless in ten cases, although in six of these there was a history of colic prior to the original operation. In two cases there was no colic, and relatively little pain. In general, the jaundice came on at longer intervals after the first operation than in cases of stricture of the common bile duct, except in the presence of persisting jaundice or of persisting biliary fistula. In cases of intervals of freedom from symptoms, the relief extended from a minimum of a few months to twenty-three years, with an average interval of three years and eight months. Attacks were often multiple, the jaundice was often fluctuating, and the laboratory data and

the physical condition of the patient, except for the fistulas, correspond to those in the cases in which operation was not performed. The surgeon reported dilated gallbladders in five cases, two, at least, being inexplainable except by the stone. Most of the ducts showed various degrees of dilatation. There were varying degrees of infection, fibrosis, and adhesions throughout and about the biliary system.

Jaundice was frequently the symptom which induced the patient with stone in the common bile duct to seek relief. A considerable number of patients had had more than one attack, lasting from one or two weeks to several months. The pain was usually fluctuating and frequently disappeared at the time the patient was examined or while under observation. The intensity of the icterus also varied considerably. Frequently it was mild, the serum bilirubin varying from 2 to 5 mg. On admission, serum bilirubin of 10 mg. was not uncommon, but in a few days a decided decline occurred. Occasionally the icterus was intense, the serum bilirubin being 15 to 20 mg., but this occurred chiefly in cases of large stones, painless onset, or with associated extensive biliary cirrhosis. Duodenal drainage, if done, usually resulted in a fairly good flow of bile.

In cases of stone in the common bile duct, chills and fever usually indicate infection. Diarrhea is rare and, when present, bile in the intestinal tract seems to be absent. The liver was often slightly enlarged and tender, and tenderness in the region of the gallbladder was frequently noted. There were six cases (in fifty-nine) in which the surgeon described a distended gallbladder. In no case was this noted by the clinician. The surgeons reported a predominance of contracted, infected gallbladders filled with stones and varying degrees of infection and fibrosis throughout the biliary tract.

Conditions Simulating Stone in the Common Bile Duct

Conditions simulating stone in the common bile duct may be listed as follows: (1) cholecystitis with stones; (2) colic following cholecystectomy, (3) cholangeitis, cirrhosis and hepatitis, and pancreatitis; (4) stricture of the common bile duct, and (5) malignant lesions of the pancreas or biliary tract.

Cholecystitis with stones.—Hartman studied a group of cases of surgical cholecystitis with or without stones. In 652 cases of cholecystitis with stones a history of jaundice occurred in 207 (31.7 per cent) and in only forty-one of these was a calculus demonstrated in the common bile duct. In 375 cases of cholecystitis with calculus jaundice occurred in sixty (16 per cent). Jaundice occurred only twice as frequently when stones were present as when none were present.

In this series there are twenty-five cases of cholecystitis with stones and jaundice in which obstruction could not be demonstrated in the common bile duct. Colic occurred in fourteen cases; in one case the pain was atypical, always radiating to the left. In eight cases the onset of icterus was without pain. In two cases an ulcer type of dyspepsia had been present for seven years, in one case, often with belching, nausea, and emesis. Atypical pain consisting of momentary "catching" at the

right costal margin preceded the icterus in one case. The jaundice varied in intensity. In seven cases the serum bilirubin was more than 10 mg. The icterus was of relatively short duration as a rule, a few days to two or three weeks. The clinical diagnosis most commonly made was stone in the common bile duct, but this was not demonstrable at operation. The explanation of the jaundice in this group of cases is in some respects unsatisfactory, but infection in the biliary tract extending to the finer bile canaliculi and leading to obstructive cholangeitis or a toxic condition of the polygonal cell of the liver is the most reasonable hypothesis. In a few cases a large stone in the cystic duct compressed the common bile duct and led to the development of icterus.

Colic following cholecystectomy.—It has long been known that persistent colic follows cholecystectomy in a certain number of cases. Judd and White have emphasized the part played by residual infection of the common bile duct (cholangeitis) as an explanation and have advocated prolonged surgical drainage of the duct as an efficient therapeutic procedure.

Cholangeitis, cirrhosis and hepatitis, and pancreatitis.—Judd and McIndoe recently stressed the primary nature of cholangeitis in some cases. This may progress, become an obliterating process, and give the syndrome of stricture in the common bile duct with jaundice. Again it may progress upward into the liver and lead to hepatitis or cirrhosis. In another group of cases jaundice occurs, and exploration reveals various pathologic processes. The surgeon may have difficulty in examining the common bile duct, occasionally feeling that a calculus may have been pushed into the duodenum. In a certain number of cases cholangeitis is the chief lesion; in others extensive pancreatitis, hepatitis, or cirrhosis is the predominant lesion. In an occasional case early pancreatic or ampullar neoplasm may be present. Often these lesions are present in various combinations. They rarely occur as isolated lesions.

In this series the lesion could not be entirely localized in thirty-eight cases. Colicky pains occurred in more than 40 per cent of the cases and jaundice often recurred repeatedly. Chills, fever, and sweats were not uncommon. Atypical pains occurred at times and in some cases pain developed later. Stone in the common bile duct was the usual clinical diagnosis in this group, but in a considerable number cirrhosis of varying types seemed the likely condition from a preoperative standpoint. Cases of cirrhosis with intermittent or persisting jaundice occur, presenting repeated attacks of colicky pain suggesting stone in the common bile duct, but at exploration calculus is not encountered. A number of such cases occurred in our series. In cases of long-standing obstruction of the duct, usually from stone or stricture, considerable cirrhosis may be present and militate against the otherwise satisfactory surgical treatment of the patient. However, remarkable reparative changes can occur in the liver; we have seen several such cases. In general the results of removal of stone from the common bile duct are very favorable in spite of the extensive cirrhosis occasionally noted.

Stricture of the common bile duct.—There were forty-nine cases of postoperative stricture of the common bile duct, in all but one of which cholecystectomy had been performed. In half of the cases painless jaundice developed, in twenty-two typical colic, and in eight atypical pain. In many of the cases jaundice or persisting biliary fistula developed immediately after operation. In the remainder of the cases convalescence was satisfactory as far as is known, but jaundice of varying degrees developed, painless, with colic, or with atypical pain, on the average of about seven and a half months after the original operation. The longest postoperative period before recurrence of jaundice was two years. It is often impossible to distinguish stricture from stone in the common bile duct but a fairly definite opinion can often be ventured by considering: (1) the type of previous operation, stricture of the common bile duct practically never following cholecystostomy; (2) the length of time after operation before jaundice develops, two years or more, favoring the diagnosis of stone, and (3) the pain factor, the incidence of painlessness being much higher in cases of stricture than in cases of recurrent stones (55 and 22 per cent, respectively). In some cases in this group the surgical diagnosis was established by inference only; the adhesions were so dense and technical difficulties so great that the common bile duct could not be isolated. The part played by surgical trauma and by infection in the production of such strictures has long been debated. In our cases most of the strictures occurred postoperatively and operation was either cholecystectomy, choledochostomy, or both. This suggests that trauma must be a significant factor. In all these cases, however, varying degrees of infection were present at the time of operation. There were also a few cases in which obliterative cholangeitis is found at operation or necropsy. In these cases the ducts were reduced to fibrous cords, presumably as the result of long-standing infection, and the cases were invariably associated with considerable cirrhosis. The following case of stricture occurring after cholecystostomy may belong to this group.

A woman, aged forty-three years, had had cholecystostomy in 1923 following a two-year history of colic, and jaundice of six weeks' duration immediately preceding operation. The jaundice cleared, drainage ceased after eighteen days, and the patient was reasonably well for a year. Following this, she had recurring attacks of colic with jaundice of one to three months' duration. Operation in 1926 showed "obliteration of the common duct from the cystic duct to duodenum, forming a fibrous cord. The right upper quadrant was a mass of adhesions." Cholecystenterostomy was done. The subsequent course was reasonably satisfactory for a time, but clinical evidences eventually developed of cirrhosis, recurrent gross gastric hemorrhages, enlarged liver, and slightly elevated serum bilirubin with a direct van den Bergh reaction, suggesting that the infectious process had progressed up into the liver.

Although colic often is one of the prominent symptoms of stricture, its presence followed by icterus which clears in a short time, always raises the question of the presence of calculus. Moreover, it is unusual to find the two conditions associated. A certain degree of cholangeitis is frequently present and may be the basis of the attacks

of colic, chills, fever, and icterus that occasionally occur after plastic repair of stricture. The fact that calculi may be the basis for such attacks and should always be considered, is illustrated in the following case.

A man, aged forty-one years, was first seen in April, 1927. Three months previously he had had an acute gangrenous appendix removed. After a month he began to suffer from biliary colics and cholecystectomy was done. The gallbladder was found to contain multiple stones. Five days postoperatively slight icterus appeared followed by discharge of bile from the wound. This condition persisted. Later pain in the abdominal wall near the wound, malaise and fever developed. Drainage of a superficial abscess was performed.

On examination there was evidence of a biliary fistula and abscess of the abdominal wall. Serum bilirubin was 2.3 mg. and test of hepatic function by the dye method showed retention, graded 3. Further drainage of the abscess in the abdominal wall was necessary on two occasions, following which the infection cleared, but the fistula persisted. July 18, 1927, the fistula was explored and was found to lead into the hepatic ducts. Signs of the distal duct were not discoverable. Hepaticoduodenostomy was performed for the stricture. Shortly after the patient was dismissed, colic, chills, fever, jaundice, and vomiting developed and persisted until his return in July, 1928.

Examination was satisfactory except for slight icterus and a ventral hernia. Exploration was again thought advisable, but the anastomosis appeared in good condition. Extensive adhesions about the liver, the parietal peritoneum, and the intestines were separated, and the ventral hernia was repaired. Symptoms recurred after the patient's dismissal and progressed, leading to loss of weight and general decline in health. On his return there was icterus and slight enlargement of the liver. Exploration was again undertaken. The ducts were found packed with stones. These were removed and a T-tube inserted for prolonged external drainage. The anastomosis again appeared to be in good condition. Convalescence was excellent and the patient gained remarkably in weight and strength.

Malignant lesions of the pancreas or biliary tract.—With carcinoma of the pancreas, pain is a common symptom and may or may not be associated with jaundice. Mussey and Eusterman reviewed different groups of cases observed at The Mayo Clinic. Pain of various types may be present for several months before further symptoms present themselves or it may be a late development. Jaundice may be the first symptom or it may not occur until late in the course of the disease. Its presence or absence probably depends on the site of the malignant lesion in the pancreas and possibly on the degree of any associated infection. If the head of the pancreas is involved jaundice usually occurs early whereas if the tail or body is primarily involved, it occurs much later and pain is an earlier and more prominent symptom. Careful study of the type of pain and the time of onset may give valuable assistance in the diagnosis. In our series of thirty-eight cases, the onset of jaundice was painless in nineteen cases, but pain occurred prior to the onset of jaundice in fourteen cases. In eight cases there was colic and in six cases other forms of pain were present. In most of the cases pain persisted after the onset of jaundice and in some cases of painless onset, pain developed later. It is also probable that pain occurred later in the course of the disease in many cases.

We do not suggest that pain with carcinoma of the pancreas is uncommon; two-thirds of our patients suffered pain of considerable degree dur-

ing the course of their illnesses. However, it should be noted that the onset of jaundice was often painless (50 per cent) and that when pain was present it was frequently atypical as compared to that of biliary colic, although such typical colic occurred in five cases.

Except in cases of colic, the pain was for the most part different from that encountered with stones. There was less variation, less tendency to occur in attacks, and it was usually described as a constant dull aching or boring distress often seriously disturbing sleep. The pain was described as occurring in the middle portion of the epigastrium, in the left upper quadrant, to the left of the naval, or in the left portion of the epigastrium. In later stages, after the development of jaundice, more or less constant pain, often extending into the back and into the region just posterior to the pancreas, is common.

Other diagnostic aids may be noted. The average age in our cases was fifty-six years. Fever occurred practically as frequently as in cases of stone in the common bile duct. Diarrhea occurred in six cases, all before the onset of jaundice, suggesting obstruction of the pancreatic duct prior to involvement of the common bile duct. There was a history of more than one attack of jaundice in only one case. A single attack of jaundice, usually of a stationary or progressive type with relatively high serum bilirubin (10 to 35 mg. for each 100 c. c.) and absent (or scanty) flow of bile through the duodenal tube, is the rule. A distended gallbladder was reported by the surgeon in thirty-four cases and was felt by the clinician in twenty-four cases. An enlarged liver was frequently palpated and there was slight tenderness in the right upper quadrant. In only six cases did the surgeon observe metastases; in all cases these were in the liver.

Primary carcinoma of the ducts or ampulla occurred in nine cases. In seven of the cases the onset of jaundice was painless. In one case there was atypical pain with radiation to the left, and in one case there was colic. In general, such cases may be compared with cases of carcinoma of the pancreas, as regards history, and general and laboratory data; often a distinction cannot be made.

There were five cases of primary carcinoma of the gallbladder. Exploration only was done, and consequently the incidence of gallstones could not be accurately estimated. They were found in one case in which colic had been present for many years. In one case colic had been present many years previously. In the other three cases the symptoms began with painless jaundice. The actual cause of jaundice in these cases is usually extension of the malignancy to the common bile duct.

There were seven cases of metastatic carcinoma of the liver, primary in various organs, chiefly the stomach. In such cases, the jaundice is relatively painless in onset, but later may be associated with more or less constant pain in the right upper quadrant or back. It must always be remembered that relatively painless jaundice may be due to secondary carcinoma of the liver with a silent primary growth elsewhere, and careful search for such growth should not be omitted.

SUMMARY

Although colic is the most typical pain in disease of the biliary tract and when associated with jaundice is usually indicative of stone in the common bile duct, yet it may be absent or replaced by equivalents of much milder degree. The intermittency of symptoms and their site in the upper part of the abdomen, and the association of evidences of infection are valuable features in localizing the disease process. Moreover, typical colic may occur in other conditions and the total symptoms may simulate calculus of the common bile duct to a large extent and lead to erroneous diagnosis. Such conditions are cholecystitis with or without stones and without evidence of stones in the common bile duct, colic following cholecystectomy, stricture of the common bile duct, cholangeitis, carcinoma of the pancreas or biliary tract, and cirrhosis. Thus, although colicky attacks had occurred in approximately 80 per cent of the cases of stones in the common bile duct in which operation had been performed, they had also occurred in approximately 45 per cent of cases of stricture and in 13 per cent of cases of carcinoma of the pancreas. On the other hand, pain may be absent in relation to the onset of the jaundice in many of these conditions. Thus jaundice developed with relatively no pain in 50 per cent of cases of carcinoma of the pancreas, in 55 per cent of the cases of stricture of the common bile duct, in 14 per cent of the cases of stones in the common bile duct, and in 22 per cent of cases of stone in the common bile duct in which operation had been performed.

BIBLIOGRAPHY

[1]BOLLMAN, J. L.: Peptic ulcer in experimental obstructive jaundice. Proc. Staff Meetings of Mayo Clinic, 5:357-358 (Dec. 10) 1930.

[2]EUSTERMAN, G. B.: Carcinoma of the pancreas: A clinical study of 138 cases. Tr. Am. Gastro-Enterol. Assn. 126-135, 1922.

[3]GRAHAM, E. A., COLE, W. H., COPHER, G. H. AND MOORE, SHERWOOD: Diseases of the gallbladder and bile ducts. Philadelphia, Lea and Febiger, 1928, 477 pp.

[4]HARTMAN, H. R.: Jaundice in surgical cholecystitis without stones. Med. Clin. N. Amer. 7:89-95 (July) 1923.

[5]JUDD, E. S.: Stricture of the common bile duct. Ann. Surg. 84:404-410 (Sept.) 1926.

[6]JUDD, E. S. AND MCINDOE, A.H.: Cholangitis. Jour. Michigan State Med. Soc. 29:174-179 (March) 1930.

[7]JUDD, E. S. AND WHITE, R. B.: Prolonged drainage of the common duct. Tr. South. Surg. and Gynec. Assn. 41:159-167, 1928.

[8]MANN, F. C., SHEARD, CHARLES, BOLLMAN, J. L. AND BALDES, E. J.: The site of the formation of bilirubin. Am. Jour. Physiol. 74:497-510 (Nov.) 1925.

[9]MCNEE, J. W.: Jaundice: A review of recent work. Quart. Jour. Med. 16:390-420 (July) 1923.

[10]MCVICAR, C. S. AND FITTS, W. T.: Clinical aspects of jaundice. Jour. Am. Med. Assn. 89:2018-2021 (Dec. 10) 1927.

[11]MUSSEY, R. D.: Pancreatic carcinoma. Med. Clin. N. Amer. 3:681-688 (Nov.) 1919.

Appendiceal Oxyuriasis*

A Study of its Incidence in 20,969 Extirpated Appendices

By HAROLD GORDON, M.D., *Ann Arbor, Michigan*

THE incidence of appendiceal oxyuriasis and its etiologic rôle in the evolution of appendicitis have been subjects of widespread medical interest. In this paper, only the incidence of oxyurids in the appendix is considered, their etiologic significance being the subject of a separate communication. The present study is unique in so far as it supplies figures for a larger series and one collected over a longer period of time than any previously reported.

LITERATURE

Since Still[45] and Metchnikoff[28] first drew serious clinical attention to the subject, intestinal helminthiasis has been responsible for many reports. Notwithstanding the many studies already made, a fairly comprehensive review of the literature reveals a striking variation in the figures submitted for the incidence of appendiceal oxyuriasis. This holds true as well for the same as for different countries. In England, Still[45] reported oxyurids present in 38 of 200 consecutive autopsies on children under 12 years of age. Of this number, 25 showed parasites both in the cecum and in the appendix, 6 in the appendix only, and 7 in the cecum alone. In a second series of 100 necropsies on children between the ages of 2 and 12 years, 32 were positive for threadworms. The number of times the appendix was implicated in this series is not stated[46].

Eastwood[14] examined 123 appendices —73 operative and 50 post mortem specimens—and found oxyurids in 14 of each group. Innes and Campbell[22] found oxyurids in 17 of 100 extirpated appendices. Rendle Short[41] found "oxyurid appendicitis quite common," but does not submit exact figures of its incidence. For Great Britain, therefore, the total reported incidence is 97 in 523 appendices examined (18.5%).

In France, Brumpt[6] and Railliet[31] made extensive studies. Brumpt[6] noted oxyurids in 3.5-4% of 800 autopsies. In Broca's service threadworms were seen in 10 of 27 appendices[6]. Railliet[31] found threadworms in 14 of 33 appendices and again in 58 of 119[6]. This yields a total incidence of 11.9% for 800 autopsies and 179 surgical specimens.

The German literature is especially rich in studies on the incidence of oxyurids. Suzuki[47] investigated material from 500 autopsies and 103 appendectomies. Of the former, 38 showed

*From the Department of Pathology, University of Michigan, Ann Arbor, Michigan.

oxyurids in the cecum and appendix, or in the appendix alone, while 6 harbored the parasites in the cecum only. The operative material contained parasites in 16 instances. Fischer[16] found oxyurids in 46 of 110 extirpated and in 29 of 105 post mortem appendices. Steichele[43] reported two series; in the first series of 1023 appendectomies, oxyurids occurred 17 times, in the second series of 234 operations, 24 times.

Jaroschka[24] made a study of 148 surgical specimens and found pinworms in 28. Nicolaus[30] found oxyurids in every one of 5 appendices removed at operation. Aschoff[1], in one series, found oxyurids in 14 of 78 specimens, in another series only twice in 1000 specimens[2]. Serbinow and Schulmann[40] examined scrapings from the peri-anal folds and from the anal and rectal mucosa of asylum children. Their subjects ranged in age from a few months or less ("lying infants") to 4 years. They were able to demonstrate threadworms or their ova in 4 of 25 "lying infants", in 8 of 11 "creeping infants", and in 54 of 77 children aged from 1 to 4 years. Using the same method of repeated scraping at intervals, one of the authors[40] demonstrated the presence of oxyurids in 84.5% of 117 farmers and peasants aged from 23 to 25 years.

Japha[23], using a special glass spatula, found oxyurids in scrapings from 132 of 200 school children suspected of harboring intestinal parasites (66%). On another occasion he examined a group of 285 unselected school children and found oxyurids in 209 (73%). The same author cites the following figures of other investigators, viz: Berndt, in Jena, examined 1000 children and noted oxyurids in 76%; Goebel, in the same city, 44.6% of 1000 children; Banik, in Munich, 30.6% of 315 children; Ruotsalainen, in Finland, 31.7% of 300 children; Gottberg, in Bonn, 32% of 200 children; and Hage, 8% of 300 adults from a German rural community examined during a typhoid epidemic. That these figures would equally well hold true for the appendix itself, can hardly be proven. Yet the fact that Still[45], Suzuki[47], and Rheindorf[35] found the appendix usually implicated when the parasites were present in the intestinal tract, makes reasonable the assumption that the appendix would be involved in the great majority of the above instances.

Rheindorf[32,33,34,35] found oxyurids in 62% of 13 extirpated appendices and in numbers varying from as low as 5% to as high as 45% at autopsy, depending upon the age incidence of the hosts. Läwen and Rheinhardt[26], in Leipzig, found 9.8% of 620 extirpated appendices positive for the presence of oxyurids. Heller[20] noted oxyurids in the intestine in 23% of 611 autopsies and in "most of them the oxyurids were also present in the appendix". Baarnhielm[3], in Sweden, during the period May 1, 1905, to December 31, 1912, found 77 of 875 extirpated appendices positive for the presence of threadworm (11.3%). Brauch[5] found oxyurids in 55% of "normal" appendices examined at autopsy and in 2 of 25 surgical specimens exhibiting acute inflammation (8%). Druener's[13] figures are 48% for post mortem material and 8 of 86 acutely inflamed appendices (9%).

Liengme[27] noted oxyurids in 7 of 159 appendices showing acute inflam-

mation (4%). Riff[36], in Strassburg, found pinworms in 32% of 152 surgical specimens. Sagredo[38] examined 100 appendices removed at operation and found parasites or their ova in 41. On the other hand, Hoffman found oxyurids in only 19 of 4000 extirpated appendices, Seiffert none in 2000, Moschowitz none in 2000, and Retzlaff none in 600[33]. In summary, then, the reported incidence of appendiceal oxyuriasis for continental Europe ranges from 3.7% for 13,522 surgical to 16.5% for 2416 autopsy specimens. But if we include also the figures for intestinal oxyuriasis in vivo, we obtain an aggregate incidence of 14.7% for 19,768 appendices and even this figure is probably a conservative reflection of the actual incidence.

Statistics for the North American continent are not nearly so plentiful. Cecil and Bulkley[8] examined 148 unselected appendices of children between 2 and 15. Their series was made up of 129 surgical and 19 autopsy specimens. They found oxyurids in 3 of the necropsy and in 17 of the surgical cases. They also noted oxyurids in 4 appendices removed from adults. Harris and Browne[19] found threadworms in 22 of 121 consecutive appendices received for routine diagnosis. Garlough[17] recorded 4% positive for pinworms. Schloss[39] made a careful study of the incidence of helminthiasis in children from New York's East Side. His subjects, ranging in age from 2 to 12 years, were divided into two groups. The first group comprised 30 subjects complaining of symptoms suggestive of helminthiasis. Twelve members of this group harbored parasites or their ova. The second group, made up of 280 unselected children, exhibited oxyurids in 22 instances. The author felt, however, that his figures failed to reveal the true incidence, since he had to content himself with single examinations of small stool specimens, and it is an accepted fact that a single negative stool examination is not conclusive.

Erdmann[15], during the two year period, January, 1902, to December, 1903, removed 201 appendices; 22 of these came from children under 10, complaining of acute symptoms and of this number 4 contained oxyurids. Crile[9] fails to record the finding of a single oxyurid in 1000 appendectomies. Ney[20] found oxyurids in 3 of 100 appendices removed at operation. Hanley[18], reporting an appendix filled with threadworms, says it is the first he had seen in 500 operations. Deaver[10] found oxyurids once in 500 appendectomies on children, while Deaver and Ravdin[11] noted oxyurids in not quite 1% of another series. Stiles and Garrison[44] examined the feces of 123 children under 15 years of age and found oxyurids in 2 instances. Castellani[7] quotes Garrison's figures for the incidence of oxyuriasis in the Philippine Islands (8%) and Dobson's figures for India (15.37%). Wood[51], in Australia, reported oxyurids present in 7 of 57 extirpated appendices. These statistics suffice to show that appendiceal oxyuriasis occurs the world over, though with varying frequency.

Material and Methods

The present series consists of 20,969 appendices received for routine diagnosis at the Pathology Laboratories of the University of Michigan during

the period July 1, 1894, to December 31, 1930. Only surgical specimens have been included. As will be shown, autopsy specimens are not necessary as controls. A few specimens received in an unfixed or dried up condition, are not included. The bulk of the material under review was derived from residents of Michigan, although a small proportion was sent in from neighboring and even from distant states. A part of the material was removed in hospitals of outlying cities and towns, the remainder at the University Hospital. The entire series, made up as it is of unselected specimens from patients of both sexes, all ages, urban and rural communities, represents an excellent cross-section of the appendices of this state.

The appendices were received ready fixed in a 10% aqueous solution of formol. After being examined grossly, they were cut into small blocks for paraffin impregnation. Staining was done with hemalum and eosin by the celloidin sheet method. During the past 23 years the blocks have been routinely selected to include representative portions of the proximal, mesial, and distal thirds of the appendix. Prior to 1908 the organs were sectioned at one or two points only. Duplicate sections were made in every case. Serial sections were not attempted since the material was received for routine microscopic diagnosis. However, the very size of the series tends to distribute the possible errors of the method and renders the study of statistical significance. In this connection, it is of interest to record that when oxyurids were found, they occurred in groups of considerable numbers, so that while one block often showed a marked numerical preponderance of the parasites, the other two blocks seldom were completely devoid of worms. Numerous workers have commented upon a similar grouping of the parasites, Still[45] finding them most frequently in the proximal, other writers nearer the distal third. The diagnosis for the entire series, with few exceptions, were made by Dr. A. S. Warthin in person, the writer being privileged to have access to the files. In no instance was an opinion recorded by other than experienced assistants.

Relationship to Age and to Sex

In Table 1 is recorded the distribution of the positive appendices, arranged according to the age and sex of the hosts. Of the 20,969 appendices examined, 221 contained oxyurids (1.05%). Calculated for each sex, the percentage incidence is 1.26% for females and .74% for males. Even allowing for the larger number of appendices received from female patients, the percentage figures show a significantly higher incidence in female than in male patients. This holds true even when we contrast the absolute and percentage incidence figures for the two sexes where the ages are given. Thus, during the age period of 2 to 46 years, 6106 appendices received from female patients revealed oxyurids in 86 instances (1.4%), while 3690 appendices received from male patients contained oxyurids in 37 instances (1%). The increased frequency of oxyuriasis in females may have some bearing on the mode of infection. Several authors (Fisher[16], Steichele[43], Ssolowjew[42], Wilhelmi and Quast[50], and Harris and

TABLE 1.

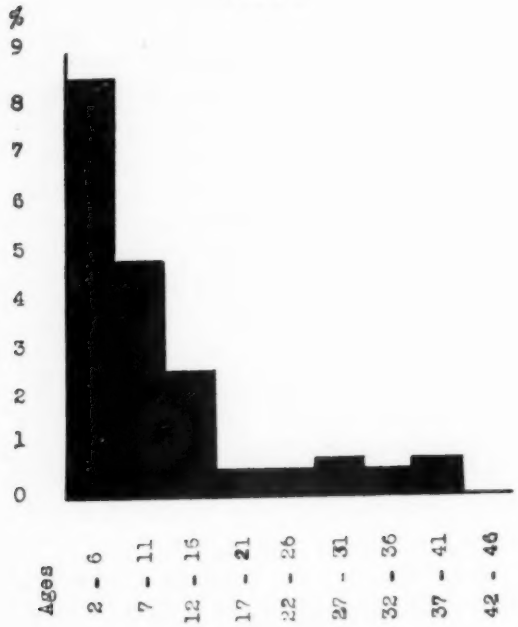
Age Groups	Males		Females		Both Sexes		Sex not Stated	Total Appendices
	Total	Oxys.	Total	Oxys.	Total	Oxys.		
Not Stated	3307	16	6555	80	9862	96	324	10,186
0-23 Mos.	5	0	2	0	7	0	1	8
2-6 yrs.	99	9	74	6	173	15	4	177
7-11 yrs.	226	10	237	12	463	22	4	467
12-16	374	6	701	21	1075	27	0	1075
17-21	797	3	1375	12	2172	15	13	2185
22-26	732	2	1191	12	1923	14	12	1935
27-31	552	5	915	9	1467	14	4	1471
32-36	404	1	726	4	1130	5	5	1135
37-41	297	1	500	6	797	7	2	799
42-46	209	0	387	4	596	4	6	602
47-51	158	0	245	0	403	0	10	413
52-56	98	0	147	0	245	0	2	247
57-61	54	0	81	0	135	0	0	135
62-66	37	1	45	0	82	1	0	82
67-71	15	1	18	0	33	1	0	33
72+	12	0	6	0	18	0	1	19
TOTAL	7376	55	13205	166	20581	221	388	20969

Age and sex incidence of oxyuriasis of all patients, calculated at 5 year periods.

Browne[19]) have recorded similar results, though a few authors have reported a slightly higher incidence among male patients.

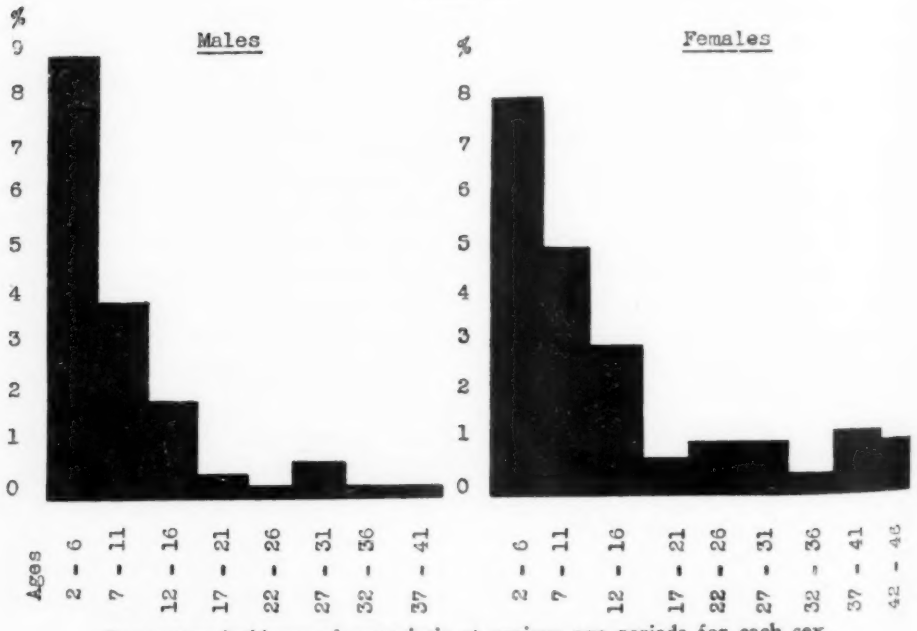
The relative frequency of oxyuriasis in the two sexes is related also to the age incidence of the hosts. In this study the age groups are recorded for five year periods. These periods have been selected to correct for the well-known tendency of patients to "favor multiples of five and, in lesser degree, the even years in giving their ages" (Weller[49]). In Table 1 we note that where the ages are stated, the highest incidence of oxyuriasis occurs during the age period 12-16, with the age period 7-11 in second place numerically. The total incidence for the various age groups, however, hardly reveals the true facts, because of the great variation in the number of appendices received from each age group. To correct for the discrepancy in numbers, in Table 2, the percentage incidence of oxyuriasis has been calculated for each group and plotted in the form of a graph. Stated in this manner, the relationship between the age of the host and the occurrence of oxyuriasis becomes immediately apparent. Thus, from a peak of 8.5% during the age period 2-6 years, there is a rapid decline to 4.7% during the second half of the first decade, with a further fall to 2.5% for the period 12 to 16 years. From the 17th to the 46th year the percentage incidence varies but little, while after the 46th year appendiceal oxyuriasis is almost unknown in Michigan. These findings are once again in accord with previously reported studies. Comparing the sex and age percentage incidence figures (Table 2*a*) we find that oxyuriasis is persistently more frequent in females than in males after the 6th year, with a much less abrupt decline for the three five year periods from the 2nd to the 16th year and with a more evenly maintained distribution from the 17th to the 46th year. As will appear later, the more frequent mani-

TABLE 2.



Percentage incidence of oxyuriasis at various age periods for both sexes.

TABLE 2A.



Percentage incidence of oxyuriasis at various age periods for each sex.

festation of oxyuriasis in children is probably related to the mode of infection. In passing, it is an interesting coincidence that both the oldest and the youngest case of oxyuriasis occurred in males, aged 69 and 2½ years respectively.

Seasonal Incidence

Inquiry into the possibility of a seasonal predilection reveals that the monthly variations in the occurrence of helminthiasis (Table 3) are not greater than can be accounted for by chance

TABLE 3

Monthly and seasonal incidence of oxyuriasis.

December	18	
January	18	
February	19	
		55
March	11	
April	16	
May	17	
		44
June	23	
July	16	
August	27	
		66
September	24	
October	18	
November	14	
		56
	221	221

distribution and the observed fact that more appendices are received for section during the second half than during the first half of the year. Nor is the seasonal incidence sufficiently varied to be statistically significant. This phase of the problem is intimately bound up with the wider ones of the probable persistence of infection and of an equally probable delay in the manifestation of symptoms. The frequent finding of mature forms; the occurrence, side by side in the appendix, of adult and of young worms; the occurrence of female worms filled with ova; the occasional presence of ova only; all the facts speak for chronicity of infection. It is therefore not unlikely that the symptoms, reflex and direct, are a poor index of the date of infection and much more probable that they lag far behind the initial occurrence of oxyuriasis, thus affording the parasites time to complete a greater or lesser period of their life cycle before discovery.

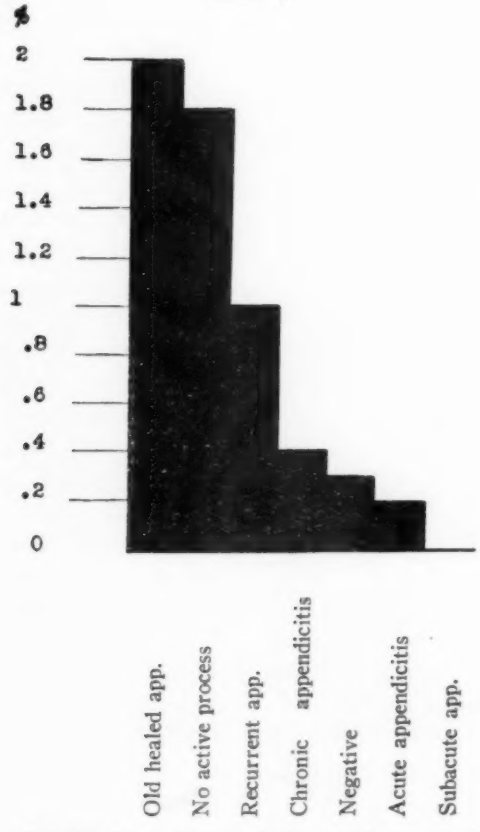
Relationship Between Oxyuriasis and Appendicitis

This phase of appendiceal oxyuriasis will be discussed in detail later and is here touched on only briefly. That there is a relationship between oxyuriasis and appendicitis, has been fully discussed both pro and con. The very large number of single case reports is mute evidence of the interest and significance attaching to this phase of the problem, with Rheindorf[32,33,34,35] and Aschoff[1,2] playing leading rôles in the controversy. In Table 4 is plotted the percentage incidence of exyuriasis for each of seven types of appendices most frequently involved. This list includes not only some of the well recognized types of inflammation, but also groups of appendices whose exact place in the general pathology of the appendix may not be immediately apparent. These diagnosis are in keeping with Warthin's dictum that "a full and adequate analysis - - - - - - - is of more objective

value than the bare diagnosis"[48]. Accordingly, the appendices showing hyperplasia of the lymphoid tissue, fecal concretions, dilatation of the lumen, atrophy and chronic catarrh of the mucosa, or any combination of these changes, are classified as showing "No active process." The appendices failing to show even such slight changes as listed above, are grouped as "negative." These are, to all intents, "normal" appendices. A sufficiently large number of appendices of this type are included to render unnecessary the use of autopsy material for control purposes. The limitation of this study to surgical specimens introduces fewer variants and allows a more accurate analysis of the factors entering into the causation of oxyuriasis. The appendices showing an increase of connective tissue of the submucosa are grouped under the title "Old healed appendicitis," the old fibrosis constituting the only indication of the obsolete inflammation.

The percentages recorded in Table 4 show a significant relationship be-

TABLE 4.



Relationship of oxyuriasis to the general pathology of the appendix.

tween the presence of oxyurids and the type of appendix harboring the parasite. Oxyurids were seen most frequently in the group of appendices showing an old healed inflammation (2%) and next most frequently in those showing no active process (1.8%). The appendices showing evidences of recurrent inflammation were affected in 1% of their number. The chronically inflamed organs, the frankly negative, and the acutely inflamed ones show a closely similar percentage incidence, while in no instance were oxyurids found in association with subacute appendicitis. Not only do the percentage figures show a significant association between oxyuriasis and appendices devoid of active inflammation, but by actual count oxyuriasis occurs more than twice as often in the inactive appendices as in the actively inflamed organs. This finding is somewhat in line with the recorded observation that native Chinese show a high incidence of helminthiasis, yet rarely exhibit acute appendiceal attacks. Here, however, we must not lose sight of such modifying factors as a stoical disregard of pain and difficulty of access to competent surgical and diagnostic attention.

The Increasing Incidence of Appendiceal Oxyuriasis

The increasingly frequent observation of oxyurids in appendices received for routine diagnosis during recent years primarily was responsible for the initiation of this study. That this observation is not merely an impressionistic one is proved by the objective data furnished in Table 5. In this table are recorded the total appendices received, calculated for five year periods, from 1894-1930, with the total and percentage incidence of oxyuriasis for each of these periods. Except for the initial and the final periods, the percentage incidence is surprisingly similar. That appendiceal oxyuriasis is on the increase in Michigan can hardly be gainsaid. This is even more strikingly evident when we contrast the figures, absolute and percentile, for the two periods 1894-1925 and 1925-1930. In each case the figures are computed as from July 1st to June 30th, except for the year 1930, in which the figures up to December 31st are included. Up to June 30th, 1925, 5,572 appendices were sectioned and oxyurids were present in 23 instances (.41%), while since June 30th, 1925, threadworms were present in 198 of 15,397 appendices (1.28%).

TABLE 5.

Year Period	Total Appendices	Total Oxyurids	Percentage Oxyurids
1894-1900	32	0	0.00
1900-1905	304	1	.33
1905-1910	319	1	.31
1910-1915	624	2	.32
1915-1920	1817	6	.33
1920-1925	2476	13	.52
1925-1930*	15397	198	1.28
Totals	20,969	221	1.05

*December 31, 1930.

Total appendices, incidence, and percentage incidence of oxyuriasis, calculated at five year intervals, 1894-1930.

Such a decided increase can hardly be attributed to coincidence and must surely be bound up with the larger problem of the usual method of infection.

Comment

How can this relative and absolute increase best be accounted for? At an early stage of this study an attempt was made to segregate the urban and rural cases. Such a distinction, however, is hardly valid for a state as closely settled as Michigan, and one, moreover, where an abundance of automobiles and of good roads make for a free commingling of the entire population. Therefore, whatever the cause for the increase, it can be attributed only to factors operating in town and country alike. While the past decade has seen a very considerable increase in the population of Michigan, there has been but little change in the average composition of its people. An altogether negligible number of these appendices were derived from the Detroit area or from the other large manufacturing centers. These are the areas which have seen the largest influx of aliens and the most marked rise in population. The bulk of the appendices were sent in from communities showing a steady rather than a phenomenal increase in numbers. Increased immigration can therefore not fairly be blamed for the increased incidence of oxyuriasis. Probably the biggest single change in habits during the past decade, other than those occasioned by improved methods of transportation and communication, has been in habits of diet. In earlier years, meats, cooked vegetables, dairy products, and bread furnished the staple foods. Now popular fancy, intrigued by the romance of the newly discovered vitamins, and under the urge of advertising, demands a plentiful supply of accessory food factors in the daily menu. Raw fruits and fresh vegetable salads, at one time reserved for a few educated palates, now figure prominently in the bill of fare of most homes. Improved refrigeration and marketing facilities have aided materially in increasing the consumption of leafy vegetables and fresh fruits. Thus, while the estimated population of Michigan has increased from 3,668,412 in 1920, to 4,283,860 in 1925, and to 4,591,000 in 1928, the cultivation of fruits and vegetables for consumption has in some instances doubled, in others tripled, only a few products being produced to a lesser extent during the stated periods. In addition to the increased home production of perishable fruits and vegetables, there has been an even more marked increase in the importation of such foods from other states. That this change in diet may indeed be an important etiologic factor, is indirectly attested to by the greater frequency with which seeds and coarse vegetable fibers are seen in "modern" appendices. Moreover, infection through contaminated fruits and vegetables affords a logical explanation for the observed greater frequency of oxyuriasis in females than in males, and in children than in adults. Women are more commonly concerned in the preparation of meals than men, hence more apt to come in contact with infected foodstuffs; and children are less apt to be observant about exact and careful preparation of the leafy vegetables than are adults.

The sparsely known facts of the life cycle of *Oxyuris vermicularis* do not refute the above hypothesis. Castellani[7] states that the threadworm is parasitic only for man. Wilhelmi and Quast[51] demonstrated oxyurids in cockroaches and in mice, but were able to distinguish these from the human parasite by the constantly larger size of the latter. During a period of fifteen years spent in the analysis of more than a thousand samples of water, these authors were unable to find oxyurids or their ova in a single sample. They therefore do not favor contaminated water as a likely source of infection. Nor, according to the same authors, do flies act as vectors since they could find no ova on flies confined for twenty-four hours in a glass cage with infected mice. They were equally unsuccessful in implicating the dust of schoolrooms, since they were unable to find ova in the dust, even when they had previously placed some there themselves. They, therefore, incline to Leuckhardt's theory of auto-infection. This seemed to them the most likely method, as proved by their ability to recover ova from under the nails of a high percentage of infected school-children. They tested the nails of the index, ring, and middle fingers of both hands of 1000 school children and found the test highly successful even when the nails had previously been cleaned. They also showed a relationship between the percentage of successes and the ages of the subjects. Young children (class 7A and 7B) and children in the "upper class" showed a relatively low incidence of nail bed infestation; due, probably, in the former instance to parental, in the latter to personal care of the nails. However, while this may indeed be a fruitful source of re-infection, it is difficult to conceive how it can operate in the spread of oxyuriasis from person to person.

Langhans[25] states that Leuckhardt's theory is now generally discredited. He found empty egg shells in the peri-anal folds and therefore concluded that the young larvae ascend along the intestinal canal. Still[45], noting many immature forms in the appendix and the nearby cecum and none in the small intestine, concluded that the appendix is the selective breeding ground of the parasites. The admittedly lower incidence of appendiceal as contrasted with intestinal oxyuriasis, hardly supports such a hypothesis. Drigalski and Koch[12] on the other hand, found an equal incidence (59%) of oxyuriasis in 100 children whose appendices had been removed and 100 normal controls, both groups selected at random from among 21,000 school-children between the ages of 6 and 14 years. These authors relate the occurrence of oxyuriasis to the constitutional pathology of the hosts. Of the 200 children examined, oxyuriasis occurred but once in 6 pyknic (16%), in 16 of 22 asthenics (73%), and in 96 of 172 eumorphics (55%). They relate their findings to the factor of constitutional constipation, rare in the active, well muscled pyknics, common in the ptotic, more sluggish asthenics. The longer intestinal tract of the latter favors concentration of the feces, tending towards constipation. Drigalski and Koch thus argue that the oxyurids develop and multiply in situ. Steichele[48] in commenting upon the greatly increased incidence of appendiceal oxyuriasis dur-

ing the post-war as contrasted with the pre-war periods, suggests overcrowding, poor diet, and contamination of vegetables with excreta as the most likely causes of the increase. Bass[4] believes that self-infection and contamination of fruits and vegetables are the usual methods of acquiring the disease, with the further possibility that it may also be fly-borne. She states that the eggs develop only after entering the gastro-intestinal tract and being acted upon by the digestive juices. One other factor must be considered in explaining the increased incidence of appendiceal oxyuriasis. In earlier years catharsis was a routine part of the preoperative preparation of patients, whereas now they are usually given a gentle enema. Also, while the average pre-war parent made frequent use of drastic purges for the abdominal complaints of children, the more modern mother, educated to its possible dangers, refrains from such a method of therapeusis.

Conclusions

1. In a series of 20,969 extirpated appendices, oxyurids were found in 221 (1.05%).

2. Females are much more commonly infected than males (1.26% and .74% respectively).

3. Infestation is much more common during the first decade of life than in later years and almost unknown in Michigan after the 46th year.

4. There is no significant seasonal predilection for the occurrence of oxyuriasis.

5. The incidence of appendiceal oxyuriasis is significantly greater during the past decade than during the earlier years of the period under survey.

6. The increased frequency of appendiceal oxyuriasis is probably related to the increased consumption of uncooked leafy vegetables and raw fruits.

REFERENCES

[1]Aschoff, L.: Appendicopathia Oxyuria (pseudo-appendicitis ex oxyure). Medizin. Klinik. 9:249 (Feb.) 1913.

[2]Aschoff, L.: Die Wurmfortsatzentzundung, Jena, 1908.

[3]Baarnhielm, quoted by Innes and Campbell, reference 22.

[4]Bass, Elizabeth: A consideration of some of the intestinal parasites with a report of three cases of "oxyuris incognita" infection. New Orleans Med. and Surg. Jour., 81:342 (Oct.) 1928.

[5]Brauch, M.: Ueber Appendicopathia oxyurica. Beitr. z. path. Anat. u. z. allg. Path., Jena, 71:207, 1922-3.

[6]Brumpt, E.: Précis de Parasitologie, 1913, p. 420.

[7]Castellani, A. and Chambers, A. J.: Manual of Tropical Hygiene, New York, 1919, pp. 1776-7.

[8]Cecil, R. L. and Bulkley, K.: On the lesions produced in the appendix by oxyuris vermicularis and trichocephalus trichiura, J. Exp. Med., 25: 225 (Mar.) 1925.

[9]Crile, G. W.: A summary of 1000 cases cases of appendicitis with observations on etiology. Ohio Med. Jour., Columbus, 2: 615 (1906-7).

[10]Deaver, H. C.: Appendicitis in childhood, with a report of 500 cases. J.A.M.A. 55:2198 (Dec. 24) 1910.

[11]Deaver and Ravdin quoted by Fischer, reference 16.

[12]Drigalski, W. and Koch, E. W.: Ueber die Bedeutung des Wurmfortsatzes für die Entwicklung der Oxyuren: Deutsche med. Wochenschr. 51: 309 (Feb.) 1925.

[13]Druener, L.: Ueber die Oxyuren im Wurmfortsatz. Beitr. z. klin. Chir., Tubing, 122:438, 1921.

[14]Eastwood, E. H.: The relation between appendicitis, oxyuris vermicularis and eosinophilia in the appendix wall. J. Path. and Bact. 26:69 (Jan.) 1923.

[15]Erdmann, J. F.: Appendicitis in young children, N. Y. Med. Jour. 79: 537 (Mar.) 1904.

[16]Fischer, W.: Oxyuren und Appendicitis. Deutsche Zeitschr. f. Chir. 183:222 (Nov.) 1923.

[17]Garlough, L. N.: Intestinal worms and appendicitis. J.A.M.A. 80:422 (Feb. 10) 1923.

[18]Hanley, L. G.: Appendectomy: Oxyuris vermicularis in the appendix. Buffalo Med. Jour., N.S., 43:178, 1903-4.

[19]Harris, W. H. and Browne, D. C.: Oxyuris vermicularis as a causative factor in appendicitis. J.A.M.A., 84:650 (Feb.) 1925.

[20]Heller, A.: Darmschmarotzer, V., Ziemssens Handbuch der speziellen Pathologie und Therapie, Bd. 7, 2 Halfte, 1876, quoted by Hueck, Ref. 21.

[21]Hueck, O.: Ueber die pathologische Bedeutung von Helminthin in der Appendix. Frankfurter Ztschr. f. Path. 13:434, 1913.

[22]Innes, J. A. and Campbell, A. E.: The occurrence of oxyuris vermicularis in the human vermiform appendix: Parasitology, 7:189 (June) 1914-15.

[23]Japha, A.: Die Verbreitung von Oxyuris Vermicularis bei Schulkindern. Münch. med. Wochenschr. 72:473 (Mar.) 1925.

[24]Jaroschka, K.: Ueber Typhlitis und Appendicitis verursacht durch Oxyuren. Deutsche Zeitschr. f. Chir. 183:99 (Nov.) 1923.

[25]Langhans, G. L.: Zur Biologie des Oxyuris Vermicularis. Archiv. f. Kinderheilkunde, 77:27 (Jan.) 1926.

[26]Läwen, A. and Rhinhardt, A.: Ueber das durch Oxyuriasis des Wurmfortsatzes und Appendicitis ex oxyure hervorgerufene Krankheitsbild und seine pathologisch-anatomischen Grundlagen. Münch. medizin. Wochenschr. 66:1433 (Dec.) 1919.

[27]Liengme, A.: Y a-t-il relation de cause á effet entre la presence des oxyures dans l'appendice et l'appendicite. Thèse de Geneva. 1921.

[28]Metchnikoff, L.: Rôle des helminthes dans l'appenicitie. Jour. de Pract. 15: 185, 1901.

[29]Ney, G. C.: Pinworm appendicitis. Johns Hopkins Hosp. Bull. 23:123 (April) 1912.

[30]Nicolaus, H.: Oxyuren in der Appendixwand. Deutsche Zeitschr. f. Chir. 215:133 (Mar.) 1929.

[31]Railliet, G.: Sur les parasites de l'appendice malade, Compt. Rend. Soc. de Biologie, 70:310 (Mar.) 1911.

[32]Rheindorf, A.: Die Wurmfortsatzentzundung, Berlin, 1920.

[33]Rheindorf, A.: Hysteroneurasthenie oder chronische Appendicitis? Berlin. klin. Wochenschr. 51:1211 (June), 1914.

[34]Rheindorf,, A.: Hysteroneurasthenie oder chronische Appendicitis? Berlin. klin. Wochenschr., 51:1271 (July), 1914.

[35]Rheindorf, A.: Beitrag zur Frage der Bedeutung der Oxyuren bei der Wurmfortsatzentzundung der Kinder, Berlin. klin. Wochenschr. 49:503 (Mar.) 1912.

[36]Riff, A.: Contribution a l'etiologie de l'appendicitis. Presse Med., 27:521, (Sept. 18) 1919.

[37]Ruotsalainen, A.: The frequency of intestinal parasites, especially of the oxyuris vermicularis, in children. Monatschr. f. Kinderheilk. 10:329 (July), 1912, abstr. Brit. Jour. Dis. Child. 9:329 (July) 1912.

[38]Sagredo, quoted by Innes and Campbell, reference 22.

[39]Schloss, O. M.: Helminthiasis in children. Am. Jour. Med. Sci., 139:675 (May) 1910.

[40]Serbinow, P. I., and Schulmann, E. S.: Ueber die Methode der Analabschabung zur Oxyurisdiagnose. Archiv. f. Schiffs- und Tropen-hygiene, 31:482 (Sept.) 1927.

[41]Short, Rendle A.: The causation of appendicitis. Brit. Jour. Surg. 8:171 (Oct.) 1920.

[42]Ssolowjew, N. J.: Beiträge zur Frage über die Rolle der Oxyuren in der Aetiologie der Appendicitis. Mitt. a. r. Grenzgeb. d. Med. u. Chir. 41:20 (book 1) 1928.

[43]Steichele, H.: Appendicitis und Oxyuren. Archiv. f. klin. Chir. 135:373 (Apr.) 1925.

[44]Stiles and Garrison, Bull. 28 Hyg. Lab. U.S. Pub. Health and Marine Hosp. Service, 1906.

[45]Still, G. F.: Observations on oxyuris vermicularis in children. B.M.J. 1:898 (Apr. 15) 1898.

[46]Still, G. F.: Common Disorders and Diseases of Children, London, 1927.

[47]Suzuki, K.: The rôle of oxyuris vermicularis in the etiology of appendicitis and allied pathological conditions, Surg., Gyn., and Obst., 21:702 (Dec.) 1915.

[48]Warthin, A. S.: Practical Pathology, Geo. Wahr. Ed. 2. 1921, p. 310.

[49]Weller, C. V.: Age incidence in sarcoma, Arch. Int. Med. 15: 518 (Apr.) 1915.

[50]Wilhelmi, J. and Quast, M.: Ueber die Verbreitung und den Nachweis der Oxyuriasis. Klin. Wochenschr. 4:964 (May) 1925.

[51]Wood, W. A.: Appendicopathia oxyuria Med. Jour. Australia, 1:234 (March 23), 1918.

Idiopathic Thrombopenic Purpura*

By Erastus I. Guller and John S. Lawrence, *Rochester, N. Y.*

THE symptom-complex of idiopathic thrombopenic purpura is too well known to justify the reporting of additional patients with this disease. Atypical forms of this disorder are recognized but they have received much less attention. Accordingly it has seemed justifiable to report the five cases occurring in this paper since their data illustrate some of the atypical forms of this condition. These patients demonstrate how difficult it may be in some instances to distinguish aplastic anemia from idiopathic thrombopenic purpura. They further emphasize the fact that a marked leucopenia may be an associated finding in some of the patients with this disorder as contrasted with the usual normal or increased numbers of white blood cells.

Case 1: S. B., unit number 25861, a white, male student, was admitted to the Strong Memorial Hospital July 1, 1929, because of epistaxis, ease of fatigue and dyspnea. The onset of epistaxis was three months prior to admission. The nasal bleeding was severe and was controlled with difficulty by packing. Two similar attacks had occurred at monthly intervals. For two months he had noticed that he had bruised readily and for one month ease of fatigue and dyspnea had been marked.

The family history was irrelevant.

The past history. He had measles at 10 years of age and scarlet fever at 13 years of age. He has never developed any permanent teeth. Otherwise, the past history was negative.

Physical examination. The patient was a tall, thin, pale boy, aged sixteen years. There were no purpuric spots and no fresh petechiae in the skin. There was no general glandular enlargement. The mucous membranes were pale. There was a small petechia on the posterior pharyngeal wall. The conjunctivae were very pale. The fundi showed no hemorrhages. The nose was filled with a clear mucoid material. The nasal septum was deviated to the left. There was no evidence of blood in the nasal passages. The teeth had orthodontic appliances and were deciduous. The Rumpel-Leede test was negative. The physical examination revealed no other abnormal findings of interest.

Laboratory examinations. The total red blood cell count was 3,950,000 per cu. mm.; the hemoglobin was 60.0 per cent; and the total white blood cell count was 6,600 per cu. mm. The white blood cell differential formula was: neutrophils 72.0 per cent; eosinophils 6.0 per cent; basophils 2.0 per cent; lymphocytes 14.0 per cent; and monocytes 6.0 per cent. In a fixed smear, the red blood cells showed marked achromia, and moderate variations in shape. The platelets were considerably reduced. The reticulocyte count was 3.0 per cent and rose to 12.0 per cent while iron and whole liver were being given. The coagulation time was 13 minutes. The blood clot did not retract and was very friable. The bleeding time was 16 minutes. Nine months later the red blood cell count had risen to 4,740,000 per cu. mm. and the hemoglobin value had increased to

*From the Department of Medicine, University of Rochester, School of Medicine, and the Medical Clinic of the Strong Memorial Hospital and Rochester Municipal Hospital.

90.0 per cent. At this time, the coagulation time was 17 minutes. The clot retracted very slightly and was friable. During the entire period of observation his platelets were markedly reduced in number. Urinalysis: there was a moderate amount of albumin and an occasional coarsely granular cast in the urine. There were 4-5 white blood cells per high power field. There was no occult blood in the feces.

Clinical Course: During the four weeks following admission to the hospital the patient showed marked improvement, all of the petechiae disappeared, the secondary anemia rapidly diminished, and there was a typical reticulocyte response to fresh liver and iron therapy. The stained blood smears at all times showed a great paucity of platelets. The bleeding and clotting times were constantly increased, and the clot invariably showed poor retraction and was friable. The patient was discharged improved 27 days after his admission to the hospital. Three weeks later, while swimming, the patient traumatized the anterior tibial region of the left leg with a resulting large hematoma. The patient was followed at intervals in the Out-Patient Department and when last seen 9 months after his admission to the hospital he reported that he had had no evidence of bleeding in the preceding eight months. The blood condition remained unchanged throughout this period.

Case 2: M. W., unit number 34790, a white, married female, stitcher in a shoe factory, aged 46 years, was admitted to Strong Memorial Hospital complaining of epistaxis, bleeding from the gums, hematomas of the tongue, vaginal bleeding, purpuric spots and many petechiae widely scattered over the entire body. For several months she had had a posterior nasal discharge, which had invariably been blood tinged. Two weeks prior to admission she had an attack of nausea, vomiting and diarrhea, which lasted 3-4 days. Eight days later the posterior nasal discharge contained several blood clots and the gums started to bleed freely. On the following day the skin manifestations and the blood-tinged vaginal discharge appeared. For four days she had had hematomas along the tongue margins.

The family history was irrelevant.

The past history. She stated that she "had always bruised readily". For years her gums had bled readily whenever the teeth were brushed. Seven years previously the patient had had cystitis with dysuria and hematuria. During the past six years there had been a chronic nasopharyngitis, secondary to a chronic rhinitis, punctuated by acute flareups each winter. Over the past five years, hypertension and an obstinate constipation had been present. Two years prior to her admission to the hospital she had had an artificial menopause induced by X-ray therapy. One year later she had six abscessed teeth removed. For four years the patient had been a "stitcher" in a shoe factory, where she came into slight contact with benzol. The past history was otherwise negative.

Physical examination revealed a well developed and slightly obese female 46 years old, who appeared acutely ill. There was no pallor. The skin showed numerous small and large petechiae and large purpuric areas. The mucous membranes were similarly involved. There were small petechiae in the conjunctivae. The gums were spongy and bled easily. The tongue margins were hemorrhagic. The tonsils were enlarged and contained a mucopurulent discharge from the nasopharynx. The nares showed a thin watery discharge and the turbinates were slightly enlarged. The anterior cervical glands were palpable. The heart was slightly enlarged by percussion. The aortic second sound was accentuated. There was a rough systolic murmur over the aortic area. The blood pressure was 200 systolic and 120 diastolic. The liver was palpable 1 cm. below the costal margin. The physical examination was otherwise negative.

Laboratory examinations. The red blood counts ranged between 4,400.000 per cu. mm. and 5,500,000 per cu. mm. The hemoglobin values varied from 90.0 per cent to 100.0 per cent. The white blood cell counts were consistently between 4,000 per cu. mm. and 10,150 per cu. mm. Repeated white blood cell differential counts were entirely normal. The reticulocyte count was 2.0 per cent. Examination of a fixed smear on May 1, 1930, revealed complete absence of platelets. The red blood cells were normal. Following this

the platelets were scarce in repeated fixed stained smears for 50 days, after which time they were fairly abundant. At the time of admission the bleeding time was 90 minutes and the coagulation time (Howell method) was 5 minutes. The blood clot did not retract and was friable. Seventy-one days after admission, the coagulation time (Howell method) was 9 minutes. The blood clot retracted well, was elastic and held its shape when placed on a flat surface. Urinalyses were entirely negative. An electrocardiographic report showed right axis deviation. A blood culture showed no growth in five days.

Clinical Course: The patient did not bleed profusely at any time while under observation, and all hemorrhage stopped within a few days. The petechiae and purpuric manifestations rapidly cleared. No foci of infection were found. The patient was afebrile while under observation, with the exception of three days when she developed rubella.

Case 3: J. S., unit number 24698, a white male tailor, aged 28 years, was admitted to the Rochester Municipal Hospital on May 17, 1929, complaining of epistaxis, bleeding from the gums, weakness and dyspnea. The onset was eighteen months before admission to the hospital and was characterized by oozing of blood from the gums. Following this there were intermittent periods of severe epistaxis up to three weeks before admission to the hospital, since which time there had been almost constant bleeding from the nose and gums. Weakness and dyspnea were associated symptoms. There had been no contact with benzol in his work as a tailor.

The family history was irrelevant.

The past history. He had a bilateral turbinectomy without undue bleeding 4 years before his entry to the hospital. Two and a half years later he had pneumonia and following this an abscessed tooth was extracted. For eighteen months he had had several acute upper respiratory infections. The past history was otherwise irrelevant.

Physical examination revealed a well developed and nourished adult Italian male, who was very pale. His skin showed many petechiae over the trunk and extremities. There was a positive Rumpel-Leede phenomenon. The ear drums showed a few petechiae in Shrapnell's membrane. Both nostrils were filled with blood. There were two small areas of ulceration on the left side of the septum and an encrusted area 1 cm. in diameter in a similar area on the right side. There were small petechiae on the left wall of the posterior pharynx. The gum margins bled easily upon pressure. The liver edge was barely palpable, and the spleen was not palpable. There were no other abnormal physical signs of any note.

Laboratory data. On admission the red blood cell count was 2,200,000 per cu. mm.; the hemoglobin was 40 per cent (Sahli); and the white blood cell count was 2,400 per cu. mm. The white blood cell differential count was: neutrophils 49.5 per cent; eosinophils 0.5 per cent; myelocytes 1.0 per cent; metamyelocytes 2.5 per cent; lymphocytes 43.0 per cent; monocytes 3.5 per cent. The total red and white blood cell counts and the hemoglobin remained at essentially the same levels throughout the period of observation. Repeated fixed blood smears stained with Wright's stain revealed a marked reduction in the number of the platelets. The red blood cells showed some achromia and some variations in size and shape. Four days after admission, the bleeding time was 4.5 minutes and the coagulation time was 21 minutes, (Howell method). The blood clot did not retract and was friable. The reticulocyte count was 3.5 per cent. Urinalysis and stool examinations were negative. Gastric analysis showed a normal amount of free hydrochloric acid. The basal metabolic rate was —15 per cent. Cultures of the blood were negative. X-ray studies of the chest and teeth revealed no noteworthy abnormal findings. Two salivary counts were 970 and 870 leukocytes per cu. mm. of saliva.

Clinical Course. The patient was afebrile throughout the entire period of study. Two days after admission all bleeding from the nose and gums ceased, and the patient was completely free from further bleeding during the next eight weeks. Under fresh liver and iron therapy there was a slight rise in the hemoglobin percentage and the total number of red blood cells rose from 1,900,000 to

2,810,000 per cu. mm. This elevation in hemoglobin and in the total number of red blood cells was not maintained. There was a persistent leukopenia, and a constant great reduction in the number of the platelets. The patient was discharged in an improved condition 25 days after admission to the hospital and subsequently was followed in the Out-Patient Department. Ten weeks after admission to the hospital his gums again started to bleed, and two weeks later, several purpuric areas appeared on the legs. Epistaxis began one month following the purpuric areas.

Case 4: T. M., unit number 31519, a white carpenter, aged 45 years, was admitted to Strong Memorial Hospital Jan. 19, 1930, for relief of epistaxis, bleeding from the gums and purpuric spots. The onset was thirteen days before admission. During this period there had been almost continuous oozing of blood from one or both nostrils, and for five days prior to entry there had been rather general bleeding from the gums. At this time widely scattered purpuric spots first made their appearance. The patient ceased work ten days before admission to the hospital.

The family history was irrelevant.

The past history. At 43 years of age he had had a peritonsilar abscess. Each winter for several years, the patient had had severe "colds" which had been followed by a persistent cough lasting for several weeks.

The marital history was unimportant.

Physical examination revealed a well developed and nourished adult white man, who was anxious but did not appear to be acutely ill. He was pale and there were a few patches of widely scattered petechiae. The buccal mucous membranes and the conjunctivae were pale. There was constant oozing from the gums, the nostrils were encrusted with blood, and the posterior wall of the pharynx was streaked with blood. The spleen and the liver were palpable at the costal margin. The physical examination was otherwise negative.

Laboratory examinations. On admission, the total red blood cell count was 2,480,000 per cu. mm.; the hemoglobin was 50.0 per cent; and the total white blood cell count was 800 per cu. mm. The differential white blood cell count was: neutrophils 25.0 per cent; eosinophils 1.0 per cent; basophils 1.0 per cent; lymphocytes 44.0 per cent; and monocytes 29.0 per cent. The red blood cells showed no achromia. There was distinct anisocytosis. Numerous basophilic red blood cells were present. No platelets were found. The coagulation time was 9 minutes (Howell method) and retraction of the clot was poor. The icterus index was 6. The blood platelets remained much reduced in numbers during a period of 6 months. Five months after the patient was first seen the coagulation time was 4 minutes. The blood clot retracted poorly and was friable. The bleeding time was 12 minutes. The red blood cell count at this time was 5,200,000 per cu. mm. and the hemoglobin was 98.0 per cent, (Sahli). Following this there was a moderate drop in both the red blood cell count and the hemoglobin. The white blood cell count remained low throughout the period of observation, the highest count being 2,600 per cu. mm. 5 months after his first admission to the hospital. The average value was approximately 2,000 per cu. mm. with, at all times, a diminished percentage of neutrophils. Urinalyses were entirely negative throughout his period of observation. On four occasions there were positive guaiac tests for occult blood in the feces. A salivary count on Jan. 20, 1930, was 180 cells per cu. mm. Six months later it was 260 cells per cu. mm.

Clinical Course: Direct blood transfusions readily controlled the bleeding. The purpuric spots rapidly disappeared. After two weeks of complete freedom from bleeding, the patient again had a five day period of oozing of blood from the nostrils and gums. The only other evidence of bleeding while the patient was in the hospital was the presence of occult blood in his stools, occurring three weeks later. One month after admission to the hospital a third direct blood transfusion was given. From this time the patient made rapid subjective improvement. During his stay in the hospital the patient was afebrile after the fourth day. He received intensive liver therapy, cod-liver oil, and ultraviolet radiations. He was discharged improved 38 days after his admission. For the next two months he made steady progress. At rare

intervals he had slight bleeding lasting for several hours, and, occasionally, he noted a few scattered purpuric spots on his body. The patient resumed part time work at carpentering. However, on April 30, 1930, about three months after his discharge from the hospital, oozing of blood from the nostrils and the gums again started, and continued more or less constantly up to his readmission 5 weeks later. The physical examination at this time was essentially that of the first admission with the exception that the spleen was not palpable, and that there was a positive Rumpel-Leede phenomenon. Five days after his second admission to the hospital the patient bled profusely following biopsy of a gland in the left axilla. A direct blood transfusion of 300 cc. was required to control this. The patient again made rapid improvement. He was discharged improved 27 days after his second entry. Three weeks after his discharge from the hospital he reported that he had had almost constant oozing of blood from the gums since he left the hospital. Occasionally he had noticed a few petechiae on his arms and legs. When seen 3 weeks later he had had no further bleeding and was in good general condition.

Case 5: J. G., unit number 27308, a white messenger boy, aged 17 years, was admitted to the Rochester Municipal Hospital on August 22, 1929, on account of a fistula in ano, tiredness, dyspnea, weakness, and epistaxis. For six months he had tired easily. One month prior to his admission to the hospital he developed an ischiorectal abscess. Subsequently there was an associated fistula in ano which drained continuously up to his entry to the hospital. Epistaxis which recurred at weekly intervals, with varying intensity, had been present for one month. For two weeks the gums had showed slight oozing of blood. For several months he had noticed that he bruised easily. Tiredness, dyspnea, and weakness had been progressively more pronounced during the month preceding his admission to the hospital.

The family and past histories were irrevelant.

Physical examination. The patient was a well developed and nourished white boy of seventeen years who appeared acutely ill. There was marked pallor. Petechiae were present over the anterior chest and about the pelvis. There was one purpuric spot on the shaft of the penis. The mucous membranes were very pale. There was a large purpuric spot on the soft palate and several on the posterior pharyngeal wall. There was some fresh blood on the upper pole of the left tonsil, and on the gums. The nasal septum showed slight oozing of blood. Slight general glandular enlargement was present. There was a discharging left fistula in ano. No other relevant abnormal physical signs were present.

Laboratory examinations. Six days after admission to the hospital the red blood cell count was 2,400,000 per cu. mm.; the hemoglobin was 40.0 per cent; and the total white blood cell count was 3,800 per cu. mm. The differential formula for the white blood cells was: neutrophils 27.0 per cent; eosinophils 1.0 per cent; lymphocytes 69.0 per cent; and monocytes 3.0 per cent. The reticulocyte count was 0.4 per cent. The blood Wassermann was negative. A blood culture was sterile. The icterus index was 4. The bleeding time was 6 minutes and the coagulation time was 21 minutes. The clot did not retract in 12 hours and was friable. In a fixed smear, the red blood cells showed some achromia and slight variations in size and shape. No platelets were found. For a period of approximately 3 months the red blood cell count and the hemoglobin values were kept between 800,000 per cu. mm. and 17.0 per cent, respectively, and 2,650,000 per cu. mm. and 50.0 per cent by repeated transfusions. The total white blood cell count, the differential formula and the percentage of reticulocytes remained remarkably constant during this time. Following this, there was a fairly good reticulocyte response (6.0 per cent), after which the red blood cell count, the hemoglobin, the white blood cell count and the percentage of neutrophils increased. Seven months after the patient's entry to the hospital his total red blood cell count was 3,740,000 per cu. mm.; his hemoglobin was 84.0 per cent; and his total white blood cell count was 4,400 per cu. mm. At this time the coagulation time was 17 minutes and there was only slight retraction of the clot.

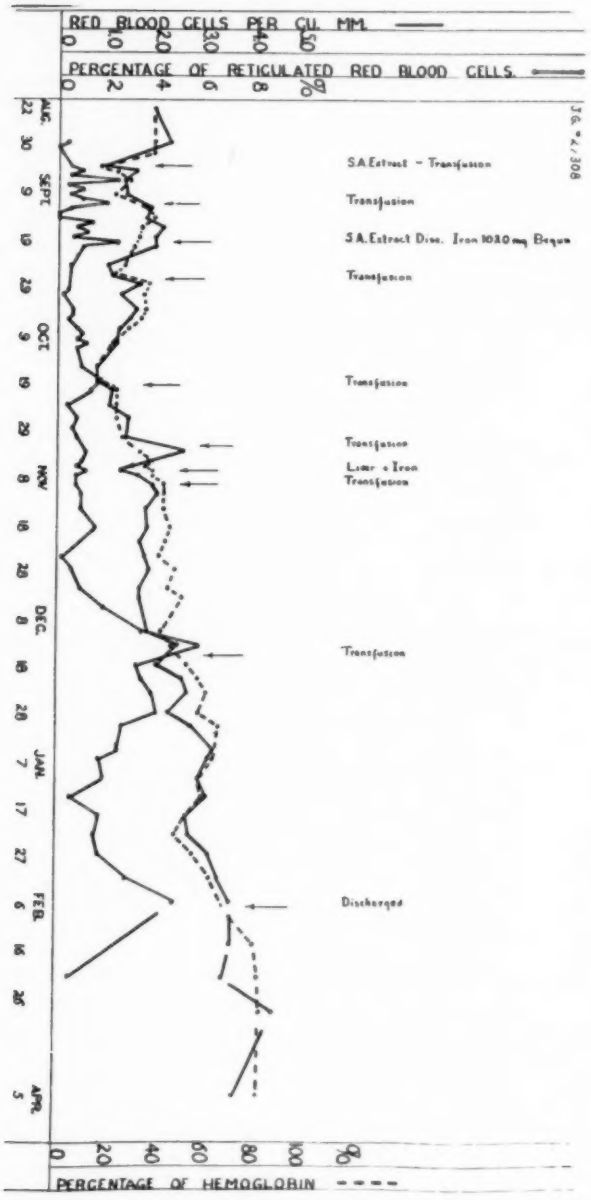


CHART I. The red blood cell count and the percentage of hemoglobin and reticulated red blood cells at various times in the blood of Case 5, J. G., unit number 27308.

Chart I shows the principal changes in this patient's blood during his period of observation. Urinalyses were negative throughout his stay in the hospital. There was a normal amount of free hydrochloric acid in the gastric contents. X-ray examinations of the chest, the sinuses and the teeth were negative.

Clinical course. The only demonstrable focus of infection was the fistula in ano, which responded rapidly to treatment. During the eight weeks following admission, the patient received four transfusions of citrated blood, of about 500 cc. each. On the second week, Secondary Anemia Extract[7] was started. On the fourth week this was discontinued, and large daily doses of iron were substituted. Under this régime there was a steady fall in the blood cell counts, from 2,850,000 to 800,000 per cu. mm., with a corresponding drop in hemoglobin percentage from 40.0 to 15.0 per cent. There was a constant leucopenia, averaging 2,000 white blood corpuscles per cu. mm. Stained blood smears showed a marked paucity of platelets at all times. The reticulocytes varied from 0.4 per cent to 2.5 per cent. The clotting time (Howell method) was prolonged. The clot failed to retract in twelve hours and was friable. During this period the patient had intermittent bleeding from the nose and gums, also several retinal hemorrhages. On the eleventh week after admission, whole liver (100 gms. daily) was started, the iron being continued as before. Over the next five weeks, four more transfusions, each of about 500 cc. of citrated blood, were given. About a month following this change in therapy, the hemoglobin percentage rose from 47 per cent, on Dec. 1, to 85 per cent on Feb. 21, and the red blood cell count increased from 1,380,000 to 3,510,000 per cu. mm., while the white blood cell count rose to an average of 5,000 per cu. mm. The platelets, at all times, were greatly reduced in numbers. The clotting time was prolonged, the clot failed to retract in 12 hours, and was friable. On the sixteenth and twenty-fifth weeks there were reticulocytic responses of 6.0 per cent and 5.0 per cent respectively. All active bleeding stopped, although purpuric manifestations on bruising, and a positive Rumpel-Leede phenomenon still persisted. The patient was discharged on Feb. 21, greatly improved. On March 6, 1930, circumcision was performed without undue bleeding. On April 5, 1930, the hemoglobin and the red blood cell count were essentially the same as in February, the platelets were still greatly reduced in numbers and the clotting time (Howell method) was 17 minutes. The clot failed to retract after 12 hours, and was friable. There had been no further bleeding.

Discussion

These five cases have one thing in common, namely, a marked reduction in the number of the platelets in the peripheral blood in the absence of any known etiological agent. No data are available that will allow any positive assertion as to the exact mechanism which is responsible for the scarcity of the platelets in the peripheral blood. As long as there remains any legitimate skepticism as to the source of the blood platelets and no satisfactory test that may be used to determine whether these elements are being destroyed in the peripheral blood, just so long must there be an inability to explain positively the mechanism which is responsible for diminished, or absent platelets in the blood of any given patient. However, correlation of various data may give strong presumptive evidence of the process at fault in some instances. For example, the presence of large amounts of invading tissue in the bone marrow in the leukemias, metastatic malignancies, and similar conditions are generally conceded to be the explanation for the diminution in platelets in the blood stream when this occurs in such conditions. Again, aplasia of the bone marrow such as is found in aplastic anemia is taken as the explanation for the reduction in the number of the platelets

in this disease. A specialized type of purpura associated with marked aplasia of the bone marrow in dogs treated with roentgen irradiation over all of the bones has recently been reported by Shouse, Warren and Whipple[6]. The fact that the megakaryocytes in the bone marrow of such dogs, have disappeared is particularly pertinent. In idiopathic types of purpura such as are reported in this paper, the evidence of bone marrow disorder may be less clear. Particularly is this true, when the platelets are the only one of the three formed elements of the blood that are involved, as is true in cases 1 and 2. Since no positive answer can be given in such cases, we shall not attempt to give any explanation of the process involved. We realize that any one of the following possibilities may be at fault in these cases. First, the platelets may be reduced as a result of diminished numbers manufactured by the bone marrow. We agree with Wright[8] that the megakaryocytes of the bone marrow are the most likely elements involved in such a process but realize that this hypothesis is not absolutely proven. Second, there may be increased destruction of the platelets in the peripheral blood. This includes the possibility suggested by Kaznelson[3] that the spleen may be actively involved in such cases. Third, there may be an increased migration of the platelets through the vascular walls. No evidence that we know of has ever been presented to indicate that such a condition exists. Fourth, there may be a combination of any of the above possibilities. Cases 1 and 2 can be explained equally well by any of these four theoretical possibilities.

Cases 3 and 4 show, in addition to a marked reduction in the number of the platelets in the blood, a diminution in the total number of the white blood cells and, in particular, a reduction in the number of circulating granulocytes. Reduction in the number of the granulocytes is frequently taken as evidence of bone marrow insufficiency as regards the white blood cell element. However, this is not a necessary explanation of such a condition. Increased destruction of these cells in the peripheral blood or increased elimination of such cells from the vascular system will satisfactorily explain such a picture. Unfortunately there is no reliable test for increased peripheral destruction of the granulocytes. Further, there is only one test that is at all satisfactory for indicating increased elimination of granulocytes from the peripheral blood. This is the salivary count as given by Isaacs and Danielson[2]. The elevation of the salivary count to twice the upper limit of normal in Case 3 indicates that this process *may* have been responsible, at least in part, for the leucopenia in this patient. Such evidence was not present in Case 4, which had a tremendous reduction in the total number of all the white blood cells and, in particular of the granulocytes. The picture present in this patient could be explained perfectly by the assumption that the white blood cell and the platelet functions of the bone marrow were reduced. No positive evidence for this assumption can be given, but on the other hand, no data are forthcoming that are inconsistent with such a state of affairs.

Case 5 had a tremendous reduction in the number of platelets in the peri-

pheral blood, considerable reduction in the total number of white blood cells and in the granulocytes, and absence of all signs of regeneration of hemoglobin and red blood cells. In other words, all of the formed elements of the blood were reduced in numbers. Unfortunately, no salivary counts were obtained in this patient. The stained smear of the blood showed no evidence of fragmentation of the red blood cells and the icterus index was low. Hence, the evidence for increased destruction of the red blood cells in the peripheral blood was lacking. No evidence either for or against increased migration of these cells from the peripheral blood is present. On the other hand, the almost complete absence of reticulocytes and polychromatophilic cells is strong presumptive evidence that the bone marrow was deficient as regards the formation of red blood cells. The simplest explanation for the whole blood picture in this case would be logically that all of the functions of the bone marrow as regards the three formed elements, were reduced or completely inhibited for a period of time. The later assumption of approximately normal values for hemoglobin, red blood cell and white blood cell counts in this patient suggests that these functions of the bone marrow recurred. The continued diminution in the numbers of the platelets may be due to any one of the four theoretical possibilities mentioned previously. It does seem, however, that in as much as there was a very good possibility of the bone marrow being involved in this case, explanation for the platelet deficiency may be found in bone marrow insufficiency.

Cases 3, 4 and 5 represent what have been termed intermediate types of purpura hemorrhagica [1,4,5]. That is they show the blood pictures which one might assume, on theoretical grounds, would be shown by patients who had conditions intermediate between true purpura hemorrhagica, as illustrated by Cases 1 and 2, and aplastic anemia. Case 5 simulates this latter condition very closely. Since the two conditions may simulate one another so closely, it may be well to emphasize this fact with reference to the difficulty in differentiating atypical forms of these conditions. A positive diagnosis of true aplastic anemia is, at best, a difficult task and is open to question as long as the patient remains alive. It would seem advisable to consider the diagnosis of aplastic anemia as questionable until a thorough trial of blood transfusions and of therapeutic measures for anemia has been given the patient. It seems highly unlikely that Case 5 would have survived had not such a procedure been adopted.

Conclusions

1. Five patients with different types of idiopathic thrombopenic purpura have been reported.

2. Various theoretical mechanisms which may be present in idiopathic thrombopenic purpura have been mentioned.

3. The close similarity between aplastic anemia and certain atypical forms of idiopathic thrombopenic purpura has been stressed.

BIBLIOGRAPHY

[1]Christian, Henry A.: The Oxford Medicine (Oxford University Press). II: 779.

[2]Isaacs, Raphael and Danielian, Arthur C.: Maintenance of leukocyte level and changes during irradiation. A study of the white blood corpuscles appearing in the saliva and their relation to those in the blood. Am. J. M. Sc., 1927, 174:70.

[3]Kaznelson, P.: Verschwinden der hämorrhagischen Diathese bei einem Falle von "essentieller Thrombopenie" (Frank) nach Milzexstirpation, Splenogene thrombolytische Purpura. Wien. klin. Wchnschr., 1916, 29:1451.

[4]Minot, George. R.: Diminished blood platelets and marrow insufficiency. A classification and differential diagnosis of purpura hemorrhagica, aplastic anemia, and allied conditions. Arch. Int. Med., 1917, 19:1062.

[5]Minot, George R. and Buckman, Thomas E.: A Text-book of Medicine edited by Russell L. Cecil. (W. B. Saunders and Co.) 1930, page 993.

[6]Shouse, Samuel, Warren, S. L. and Whipple, G. H.: Aplasia of marrow and fatal intoxication in dogs produced by roentgen irradiation of all bones. In Press, J. Exper. Med.

[7]Whipple, G. H., Robscheit-Robbins, F. S. and Walden, G. B.: Blood regeneration in severe anemia. XXI. A liver fraction potent in anemia due to hemorrhage. Am. J. M. Sc. 1930, 179:628.

[8]Wright, J. H.: The histogenesis of the blood platelets. J. Morphol., 1910, 21: 263.

Chronic Mercurial Poisoning Simulating Acute Cholecystitis and Choledocholithiasis*

(Report of a Case)

By J. William Hinton, M.D., F.A.C.S., *Assistant Professor of Surgery, New York Post-Graduate Medical School and Hospital. Assistant Attending Surgeon, Bellevue Hospital, New York City*

ATTENTION has been called during the past few years to the fact that heavy metals often cause acute toxic hepatitis which may produce symptoms quite similar to infection and calculi of the biliary tract. Arsenic, lead and mercury are the metals most frequently found in the hepatic changes and Vogel[2] has stressed the importance of examining the urine of all jaundiced patients for arsenic. In his paper it is interesting to find that in 40 jaundiced patients 34, or 85 per cent, contained arsenic in the urine, and in 9 out of 34 cases in which arsenic and jaundice occurred simultaneously death resulted. In 4 of these cases death promptly followed an operation on the biliary tract.

Myers and Throne[3] emphasized the possibility of heavy metals entering one's system through occupational sources and from water and food supplies. Lead drinking pipes are a frequent source of contaminated water, according to them, and green vegetables and raw fruits sprayed with different insecticides are another. It would seem that, in the past, patients with jaundice have been operated upon for cholecystitis and cholelithiasis without finding sufficient pathology to account for the symptoms and unquestionably some of these patients succumbed from an unrecognized metal poisoning with acute toxic hepatitis.

Case report. Male, age 33, admitted to the Fourth Surgical Division, Bellevue Hospital, June 2, 1930. *Chief complaint.* Jaundice and pain in epigastrium. *Past history.* Negative with the exception of an attack of influenza 5 years ago. *Present illness.* Six months before admission patient's attention was called to the yellow color of his skin. A short while after this he began having dull pain in the epigastrium and later the pain became more severe and he had attacks of pain in epigastrium and right upper quadrant at which time it was thought he became more deeply jaundiced. The pain was never excruciating in character, although he was never free from abdominal discomfort. At times the pain would radiate to the right lumbar region. When the jaundice was deepest the patient had clay colored stools, though they appeared normal between attacks. He lost 20 pounds in weight, 8 of them in the past 2 weeks and he had been unable to work for the past 6 weeks.

Examination. Patient was deeply jaundiced, including skin, sclera and mucous membrane. Heart normal and blood pressure 103 over

*I wish to thank Dr. Carl G. Burdick, Director of the Fourth Surgical Division, Bellevue Hospital, for the privilege of reporting this case.

60. Abdomen: slight rigidity in right upper quadrant and some tenderness on deep palpation in epigastrium, but no definite gall bladder tenderness. Liver was enlarged 3 fingers below the costal margin and there was a moderate amount of fluid in abdomen. Spleen could not be palpated. Temperature 104 on admission with 21,400 leukocytes and 86% polys. Urine: albumin 3 plus; bile 4 plus. Microscopic examination negative. Admission diagnosis of house staff; Acute exacerbation of chronic cholecystitis and choledocholithiasis. Admission note presented by the patient from the Vanderbilt Clinic dated June 2, 1930; temperature 104.8 with 26,000 leukocytes and 94% polys.

Diagnosis. Acute cholecystitis. Patient was referred to Bellevue Hospital as there were no vacancies available in the other institution. After reviewing the history it was thought the patient might possibly have a chronic metal poisoning causing an acute toxic hepatitis as he had been employed for the past several years by a carpet manufacturing company to inspect finished rugs. Laboratory work June 3, 1930, revealed sugar 80, creatinine 1.3, chlorides 525, calcium 12, phosphorus 2.5, cholesterol 272, N. P. N. 23, urea nitrogen 14. Bleeding time 7 minutes, 50 seconds and clotting time 7 minutes, 45 seconds. Icterus index 33.3. Vanden Berg indirect 3, direct 2, Fouchet 3. June 5, 1930; 24 hour specimen of urine done in Dr. Gettler's laboratory revealed a fair amount of mercury present; arsenic absent. June 9, 1930; dye test does not visualize gall bladder.

Treatment. On June 3, 1930, patient was given calcium chloride 20 c. c. of 10% solution, intravenously, and the same was repeated on the 4th, 5th, 6th and 7th. Glucose 50 c. c. of 20% solution was given intravenously on the 8th, 9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th and 17th. Sodium thiosulphate 15 grains given on the 10th, 11th and 12th. Patient ran a septic temperature for the first 5 days, temperature ranging

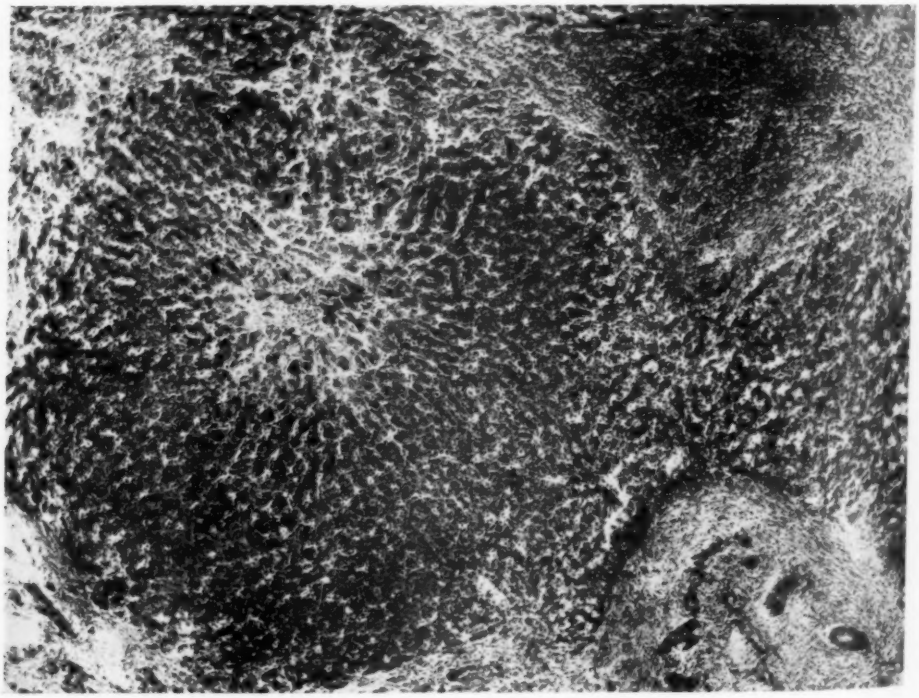


FIG. 1. Shows central necrosis with acute toxic hepatitis and chronic interstitial hepatitis at the periphery.

from 100 to 104.5. On the 6th day his temperature became normal and it was noticed at that time that the jaundice was definitely subsiding and his abdomen was not tender, nor was there any fluid present. Urine examination June 19, 1930, negative for mercury, and his jaundice had improved about 75 per cent, with a slight reduction in the size of the liver. Patient was given dilute hydrochloric acid mm. 10, T. I. D. Urine analysis on June 27, 1930, revealed a trace of mercury present. The acid was continued and the urine was positive for mercury on July 5th. He was symptom free with the exception of the slight jaundice and the enlargement of the liver. Patient again placed on calcium chloride intravenously July 6th, 20 c. c. of 10% solution, and this was continued daily until July 10th. Urine was still positive for mercury and the patient was then placed back on dilute hydrochloric acid 20 mm. Q. 4 H. His jaundice was still present but on July 17th he began running a slight septic temperature. This continued and on the 21st his jaundice had slightly deepened and he had a temperature ranging from 99 to 102. Urine positive for mercury on July 22nd but negative on July 29th. It was decided on July 29th that an exploratory operation was indicated as the patient was continuing to run the septic temperature and his jaundice was deeper than two weeks previously, but 50 per cent better than on admission. His urine was negative at this time and it was thought that a cholecystitis and choledocholithiasis might possibly be associated with the mercury poisoning. Operation August 1st. On opening the abdomen the liver was found markedly enlarged and extending 3 fingers below the costal cartilages. No nodules or irregularities detected, but it was of a reddish gray color. The gall bladder was found thickened and grossly diseased but no stones palpated in the gall bladder or common duct. Stomach and duodenum negative to palpation. Pancreas did not feel thickened or en-

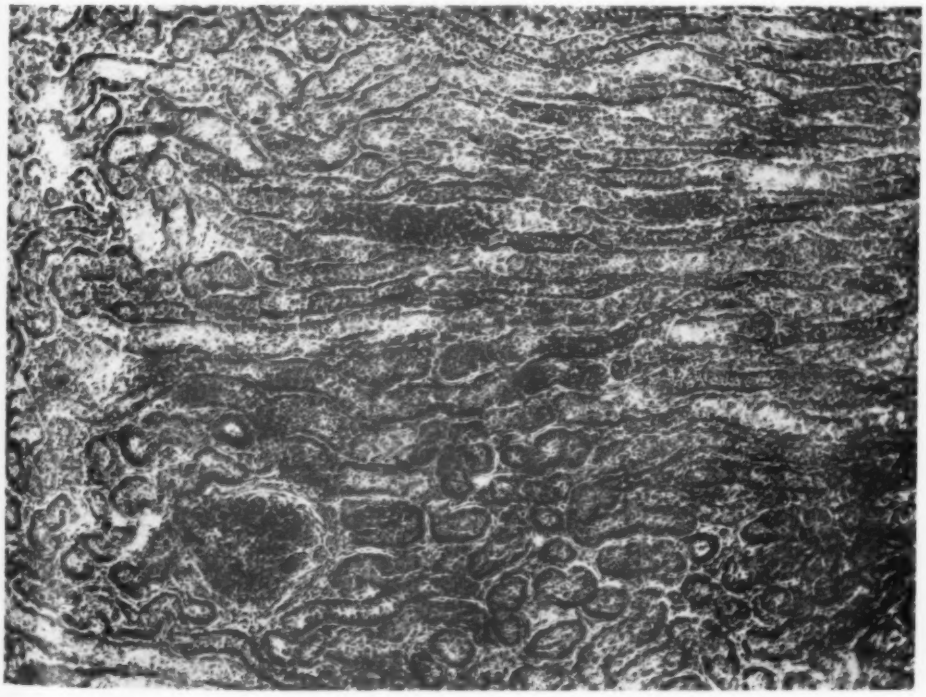


FIG. 2. Extensive degeneration and necrosis of tubular epithelium.

larged but numerous lymph glands were felt along the common and cystic ducts. Cholecystectomy done and sections taken from both right and left lobes of liver for histologic study. The liver was extremely friable and very difficult to suture and the suture cut through even when taken in mattress form. By macroscopic appearance the liver was definitely diseased. Abdomen closed in anatomical layers with a cigarette drain.

Post-operative. The patient reacted fairly well for 48 hours but then gradually declined in spite of intravenous glucose, hypodermoclysis and other supportive measures, and his death was typical of a cholemia.

Autopsy. The liver is markedly increased in size weighing 2300 gms. The capsule is

FIG. 3. Tumor seen arising around ampulla of Vater.
"A" Probe in common duct.
"B" Probe in duct of Wirsung.

unchanged. On section the liver substance is very soft in consistency and very friable. The color is a dark greenish, slate-gray. The natural lobular markings of the liver are entirely obliterated and replaced by a soft homogeneous mottling. The consistency of the liver substance is so friable as to tear easily under manipulation. There is very little fibrous tissue replacement. No metastatic nodules can be found. The microscopic appearance is illustrated in Figure I. A trace of mercury was found on chemical analysis of the liver. The kidneys are slightly increased in size and are noticeably edematous. On section the cortex and medulla are fairly well differentiated. The cortex is increased in size and edematous, pale in color with a slight violet tint and the natural markings are hazy and obscured. The pyramids are more definitely of a violaceous tint than the cortex. The markings of the pyramids are not definitely altered. The capsule strips off with increased difficulty and leaves behind it a smooth, glistening, pale, homogenous surface. The amount of fat in the pelvis is slightly increased. Figure 2 reveals tubular degeneration and necrosis. A trace of mercury was found on chemical analysis of the kidneys. Duodenum. The ampulla of Vater is markedly increased in size and appears as an irregular nodular fungating tumor mass about 5 to 6 cm. in diameter. The outer border of this mass is definitely raised, whitish in color and definitely harder in consistency than the surrounding intestine. In the center of the mass is a deep eroded depression about 1½ cm. in diameter, representing the opening of the common and pancreatic ducts. This area is of a dirty grayish color, necrotic and very friable in consistency. The base of the tumor mass extends to the outer wall of the duodenum. Figure 3 illustrates the tumor at the ampulla of Vater. In Figure 4, it is seen to be an adeno-carcinoma. The pancreas is apparently natural throughout its entire substance,

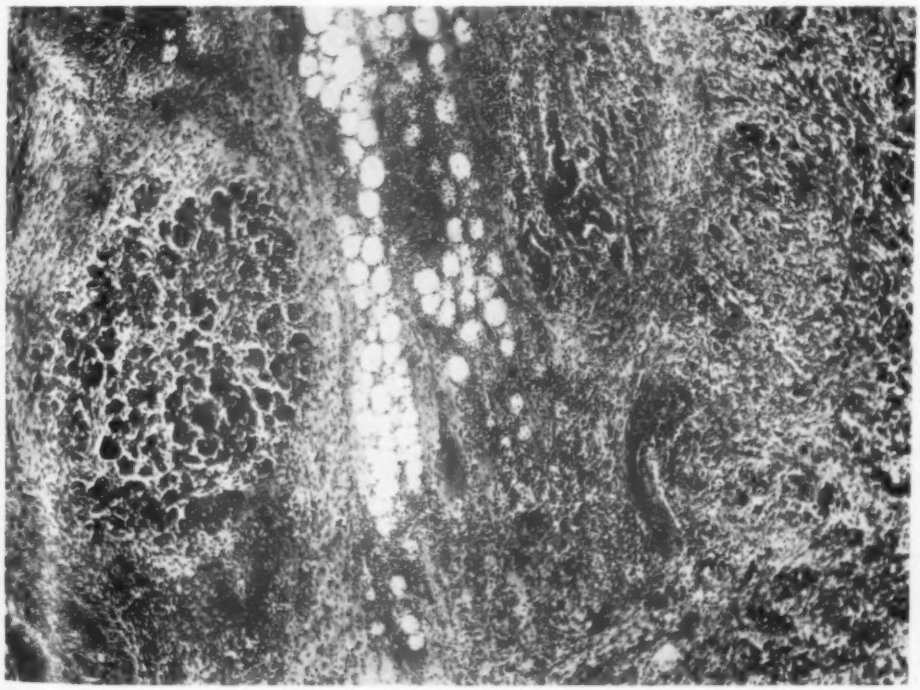


FIG. 4. Histologic section reveals the tumor, adeno-carcinoma.

showing no areas of infiltration or induration. However, it is adherent to the under side of the duodenum directly under the tumor mass and apparently attached to it. Probes can be passed through the common duct and pancreatic duct, but with difficulty. The primary cause of death was due to the mercurial poisoning with destructive liver and kidney changes. The duodenal tumor was an incidental finding.

Comment

This patient gave a history which could be interpreted as typical of a stone in the common duct with an associated cholecystitis and if measures had not been taken to rule out metal poisoning he would have been operated upon immediately. The improvement in this patient when put on calcium chloride and glucose, intravenously, was most startling. His temperature became normal in a few days, jaundice started to improve immediately after treatment was begun, and mercury was absent in urine in 16 days. Then, after placing the patient on dilute hydrochloric acid, mercury was again present in the urine, and the urine remained positive for the next 6 weeks, although he was placed back on calcium chloride intravenously from July 6th to the 19th. The urine became negative again July 29th but the patient at that time was running a septic temperature and was more deeply jaundiced.

A recent editorial[1] in the Journal of the American Medical Association called attention to the treatment of chronic mercurial poisoning by the administration of alkalis in the acute stages of intoxication, thus inhibiting the elimination of the metal from the liver and bone marrow while the symptoms of acute poisoning existed. After the acute stages of intoxication have subsided acids can be given to complete the elimination of the metal from the body which has been inhibited by the administration of alkalis.

BIBLIOGRAPHY

[1] Editorial: Journal of the American Medical Association, June 14, 1930. Vol. 94, No. 24.

[2] Vogel, Karl: "The Significance of Arsenic in the Excretions." American Journal of the Medical Sciences, August, 1928.

[3] Myers, C. N. and Throne, Binford: "The Relation of Arsenic to Public Health." New York State Journal of Medicine, July 15, 1929.

The Diagnosis of Pre-Clinical Tubercle in Suspects and Contacts by Caulfeild's Inhibitive and the T.C.F. Clinical Application:

Part II. Graphs and X-Rays*

By William E. Ogden, M.D., (Tor.), *Director, D.P.H. Chest Clinic, Toronto Western Hospital; Consultant in Diseases of the Chest, Department of Pensions and National Health, Toronto, Canada.*

In the "Annals" of October, 1930, Part I[11] of this paper gave ten points for guidance in the use of serology for diagnosis in tuberculosis, together with certain limitations. I included histories of ten examples of Tb suspects in which, at first examination no positive diagnosis could be made by any of the usual methods of clinical history, p.s. (physical signs), examination of sputum or stereo-X ray films (where obtainable). In each of these, examination of the blood serum indicated the diagnosis for or against tubercle, which diagnosis was later proved correct by positive sputum or X-ray stereograms, etc. None of the X-ray pictures and serological graphs shown on the screen at Minneapolis# were published in Part I.

I shall now give graphs or X-rays of three Tb *suspects* whose complete histories were detailed in Part I. Their stories will be understood here, without the histories. After that I shall proceed to give ten examples of Tb *contacts* complete with histories, serology and X-rays with lessons to be learned therefrom.

The Use of Graphs in the Study of Serial Serological Reactions

Since Caulfeild introduced graphs for this purpose, five years ago, we have found the significance of serial tests more easily demonstrated by this method.

The month and year of each test is noted at the top of vertical columns (see specimen below). Fifteen or twenty columns allow for the recording of the same number of tests, which are not done oftener than once a month, unless to check possible laboratory error. Fixations are noted by crosses and connecting lines in black; inhibitives by circles and connecting lines in red.

The degree of reaction is represented by horizontal lines. Fixation is record-

*These lantern slides were shown before the Academies of Medicine in Toronto and Cleveland, 1929. Final paper before the American College of Physicians, Minneapolis, Minn., February, 1930.

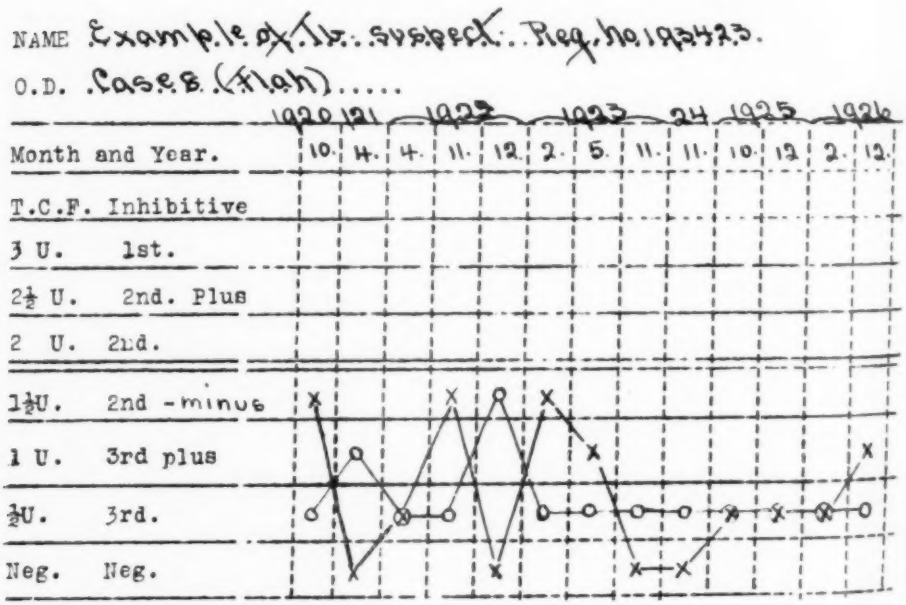
#Illness prevented me transferring these to paper for the October issue. They were given at the meeting from lantern slides and memory.

ed in half units, from a negative base line, which is the normal, to two units which is positive, and three units, very strong positive. The inhibitive is recorded in classes starting from a negative base line which is the normal in infants; then a very slight inhibitive, normal in the adult, up to second class which is positive, and first class, very strong positive. The latter reaction, viz., first class inhibitive is not common.

The terms "first and second class" originated in their prognostic significance. Tuberculous patients giving repeated second class inhibitives are as a rule doing well, at least are reacting well biologically, and inferentially, more likely to do well clinically. Those giving "first class" inhibitives do better still (have a "first class" outlook), instance case No. 3 (Mr. P.), Part I, p. 383. His two positive inhibitives were first class; although commencing with tubercle bacilli in the sputum, July, 1919, he made his cure with only moderately restricted routine, his stereos in 1920 and April, 1921, failing to show even a demonstrable lesion. But, the subject at the moment is diagnosis; the digression is to explain terminology; prognosis has been dealt with elsewhere by Caulfeild[2,7] and once by myself[3].

With these serological aids to diagnosis in our ex-soldier chest cases, since the inception of the clinic in 1918, we feel we have had unique facilities. Instance TB suspect examples Nos. 2

EXAMPLES OF TUBERCULOSIS SUSPECTS DIAGNOSED BY SEROLOGY


NAME Example of Tb. suspect. Reg. No. 193423.
O.D. Case 8. (Flah).....
1920 1921 1922 1923 24 1925 1926
Month and Year.
10. 4. 4. 11. 12. 2. 5. 11. 11. 10. 12 2. 12.
T.C.F. Inhibitive
3 U. 1st.
2½ U. 2nd. Plus
2 U. 2nd.
1½U. 2nd -minus
1 U. 3rd plus
½U. 3rd.
Neg. Neg.

Serial serological graph of suspect.

CASE 8 (Flah) was a Tb. suspect 7 years. Note 13 double tests within normal limits, then satisfactory diagnosis other than tubercle was made, viz., bronchiectasis (Part I, p. 384). This will serve also as a normal graph.

and 3 detailed in Part I, and Nos. 8 and 9 given above. In these four cases, however, the corroboration of the serodiagnosis was unusually delayed. These four were Department patients. No. 2 was an army nursing sister, later referred by Dr. Gordon Gallie, as private patient.

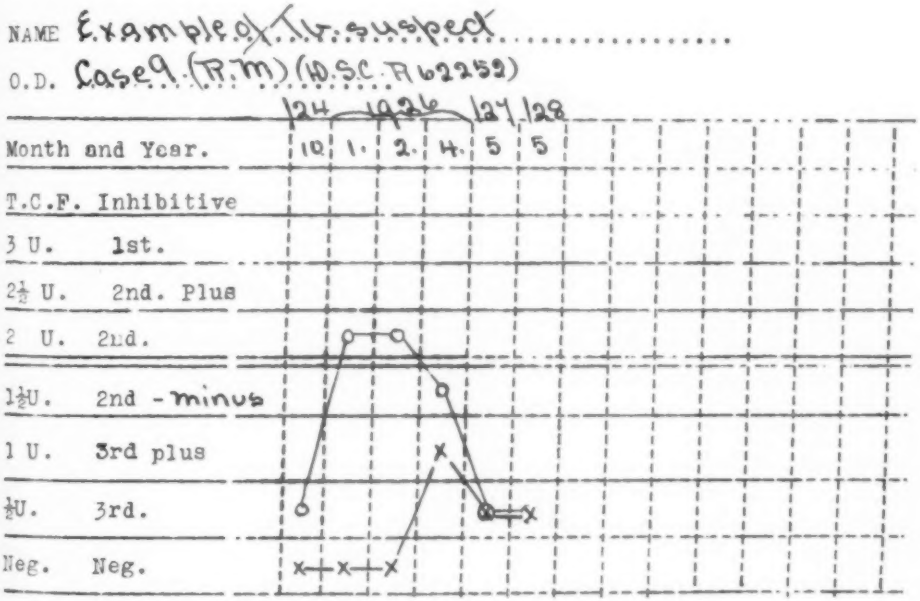
Examples of TB Contacts with Preclinical or Potential Tuberculosis Diagnosed by Serology, and Subsequently Developing Clinical Tuberculosis

I shall give ten examples of the TB contact class in which serology was of the greatest value. In half of these one might reasonably have expected the disease to have become irreparably advanced had not positive serological tests told us to hold on to the cases. It will be noted that none were followed because of symptoms.

The public is not yet "contact-conscious" (Caulfeild[12]). Four only, of my ten examples to be given, were "contact-conscious" and came on their own initiative. Three others were seized upon by the writer rather against their wish, and the remaining three were sought out as contacts by the Toronto D.P.H. follow-up system.

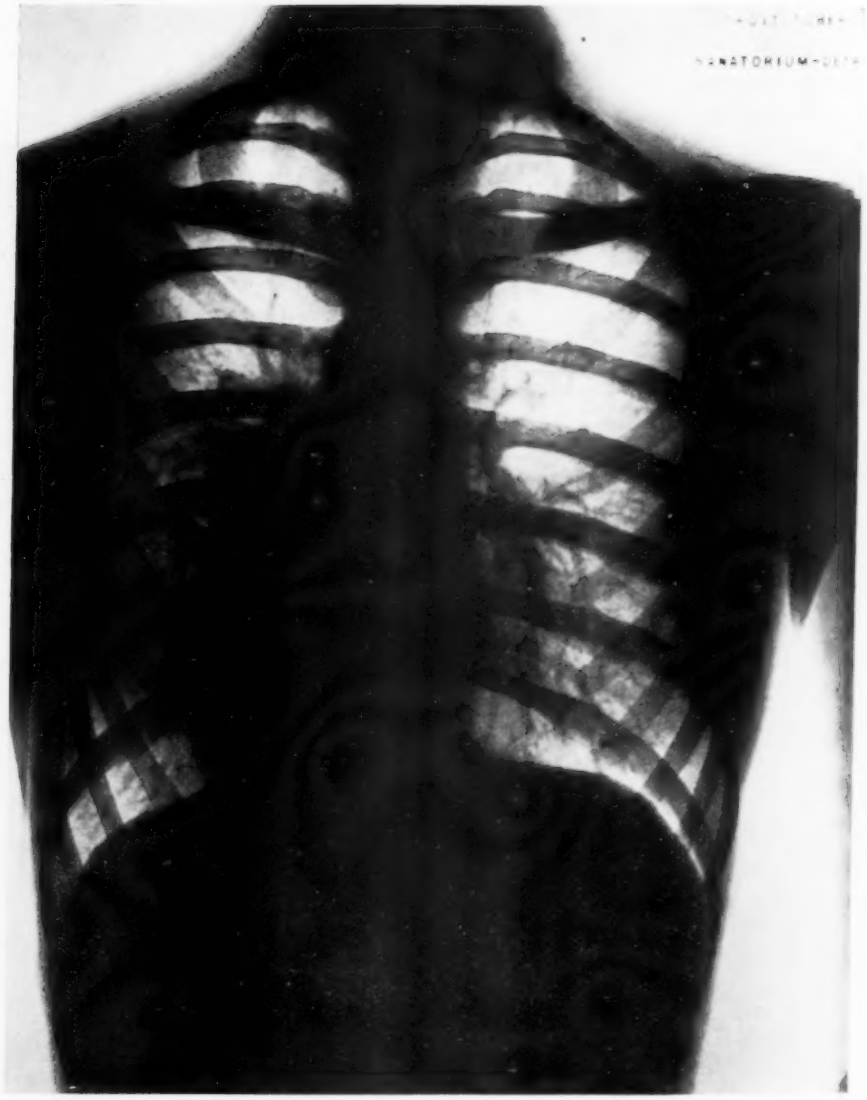
In my ten examples I have deliberately chosen seven who subsequently developed clinical tuberculosis: they are of greater interest. The actual proportion of all adult contacts developing lesions may be less than the inverse of this percentage.

Of these seven developing lesions all did so while *under my observation*, five



Serial serological graph of suspect.

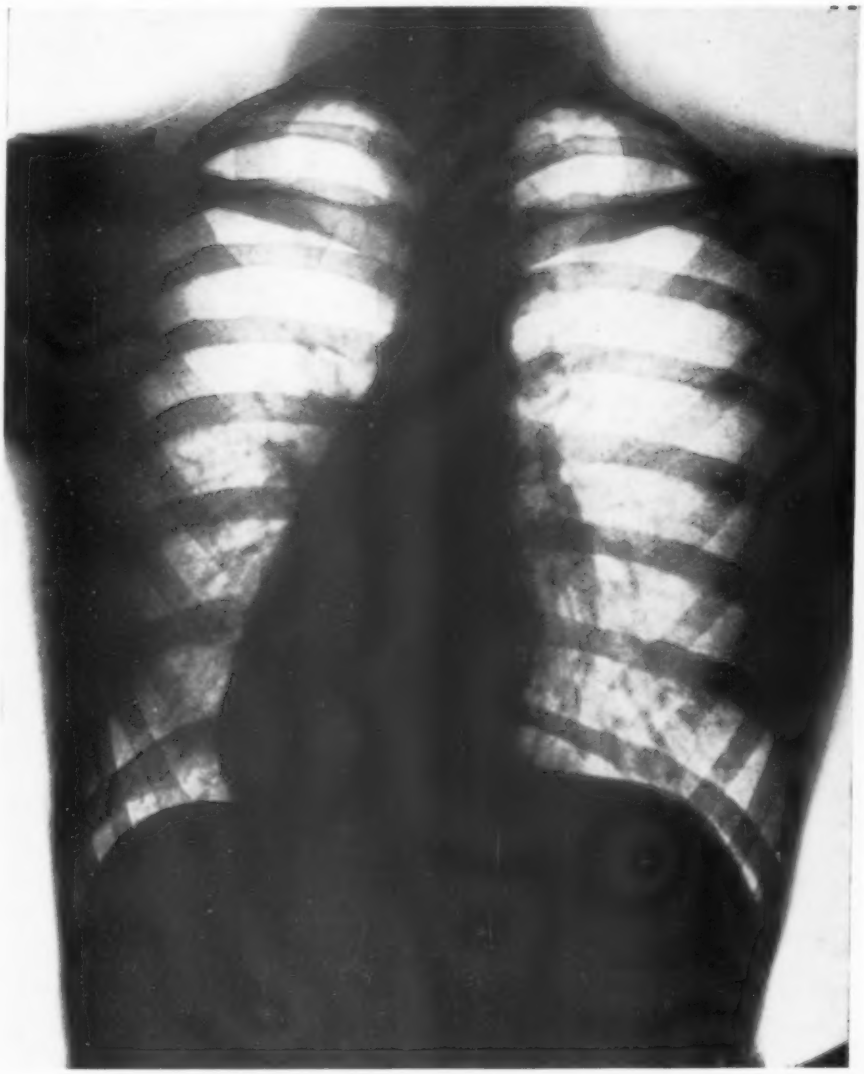
Case 9. (R.M.) showing positive inhibitives in a Tb. suspect. Serological diagnosis not proven correct till autopsy three years later (Part I, p. 384).



CASE 1. Film 1 (S.H.), 37548, June, 1928. Kindly forwarded by Dr. W. B. Howes, Detroit Tb. Sanatorium.

while continuously under my own observation. In six of these seven, I had stereograms of clear lung fields in the earlier months of observation, followed later by X-ray demonstration of definite parenchymal involvement.

As periodic adjustment of terms seems necessary, so will it also be necessary here to define and qualify certain terms which heretofore have been rather loosely used by specialists, internists and practitioners alike.



CASE 1. Film 2 (S.H.), T.W.H., July, 1928, by Dr. W. C. Kreuger, Toronto. Neither diagnostic of tuberculosis.

Diagnosed first by serology: three positive fixations, July-Sept., 1928, then tubercle bacilli found October, 1928. Complete history in Part I, p. 383, case 1 (S.H.).

All *contact-cases* were known to have *associated with* a tuberculous patient who had tubercle bacilli in the sputum. "Associated with" means more than a total of a dozen hours in the same unventilated room, with the disease present, but as yet undiagnosed, and the patient untrained. Casual meeting out of doors or visiting on an open verandah is not counted as *contact*. Recently, Alfred Henry[18] has very nicely defined, qualified, and

given examples of what is "known as a contact" and what is "not considered" such.

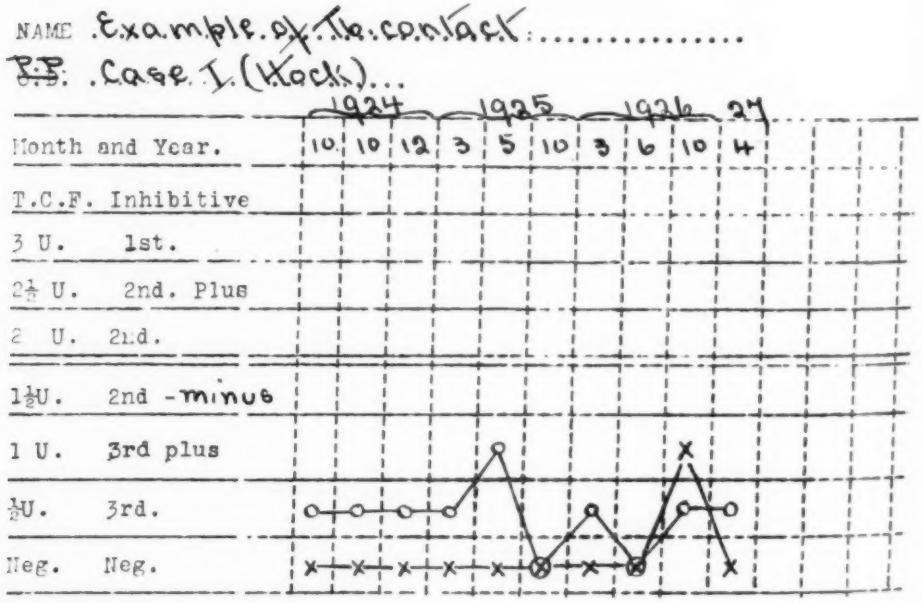
For teaching and for charting purposes I have found it necessary also to estimate and qualify the size of the dose of infection available for inhalation or ingestion by the contact. In talking to students or nurses I have referred to the daily, weekly or monthly dose of tubercle bacilli available for most city dwellers, as *minimal*. If a worker at the same desk or bench, or a boarder at the same table, is discovered to have open tuberculosis, the dose of infection is spoken of as being *gross*. If a room-mate, consort or fiancé, then the dose is *massive*. The exposure under these three different circumstances could, in other terms, be spoken of as *casual, frequent* and *intimate*, respectively.

If we now were to attempt to estimate what these terms might correspond to in figures, say *tens, hundreds* or *thousands* of live tubercle bacilli, we should truly be making a rough guess. Numbers need not concern us here as we are interested only in the relative size of possible dose.

I have not yet been able to find a suitable single descriptive word for the *infector*, the source of infection, the contaminator, the associate who is a careless or untrained open case of pulmonary tuberculosis.

Description of X-Rays

The "Caulfeild-Richards[14] (C-R) classification of stereograms of the chest" in use in the five X-ray laboratories most frequently quoted in these papers is adopted here as being, in our opinion, the most exact in anatomical



Serial serological graph of contact.
Case I. (Hock.) Showing both tests negative throughout.

extent or volume of disease, and therefore the easiest to revisualize in the mind of the reader.

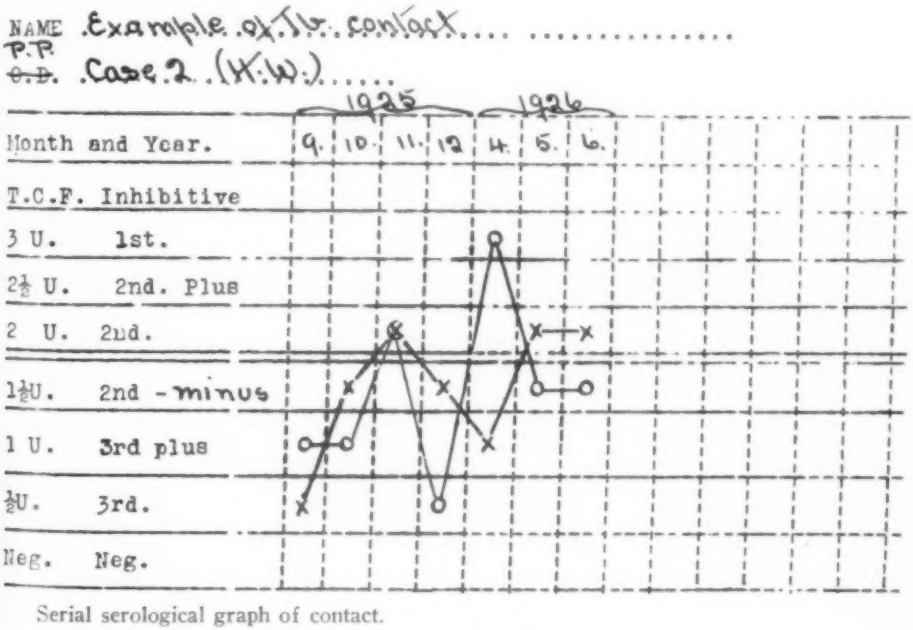
Contact-Cases With Histories, Serological Records and X-Rays

Case 1. (Hock) Kept house for brother who coughed two years, and whom I sent to Waterloo County Sanatorium, August 1923, with B.t. present and classed according to X-ray "C-R extensive 1st degree". The sister, the contact-case was 'corralled' by me October, 1924. Graph herewith shows that I refused to believe her serum would not react till I had 10 double negatives and 2 clear stereos in 3 years (20470 Kruger). I had classed her as a contact to gross doses. Would I have found positive reactions if I had tested her earlier than 14 months after exposure?

Case 2. (H.W.) The wife of the contact was attended by me for four years and at her death in 1919 from Tb. The husband-contact reported 1925, symptoms not significant (Dr. Wm. Goldie). His graph herewith shows one or both tests positive in four of a series of seven. This was 6 and 7 years after the last exposure which had ended in 1919. No lesion demonstrable in two pictures (Kruger T.W.H.). Business removal interrupted observation.

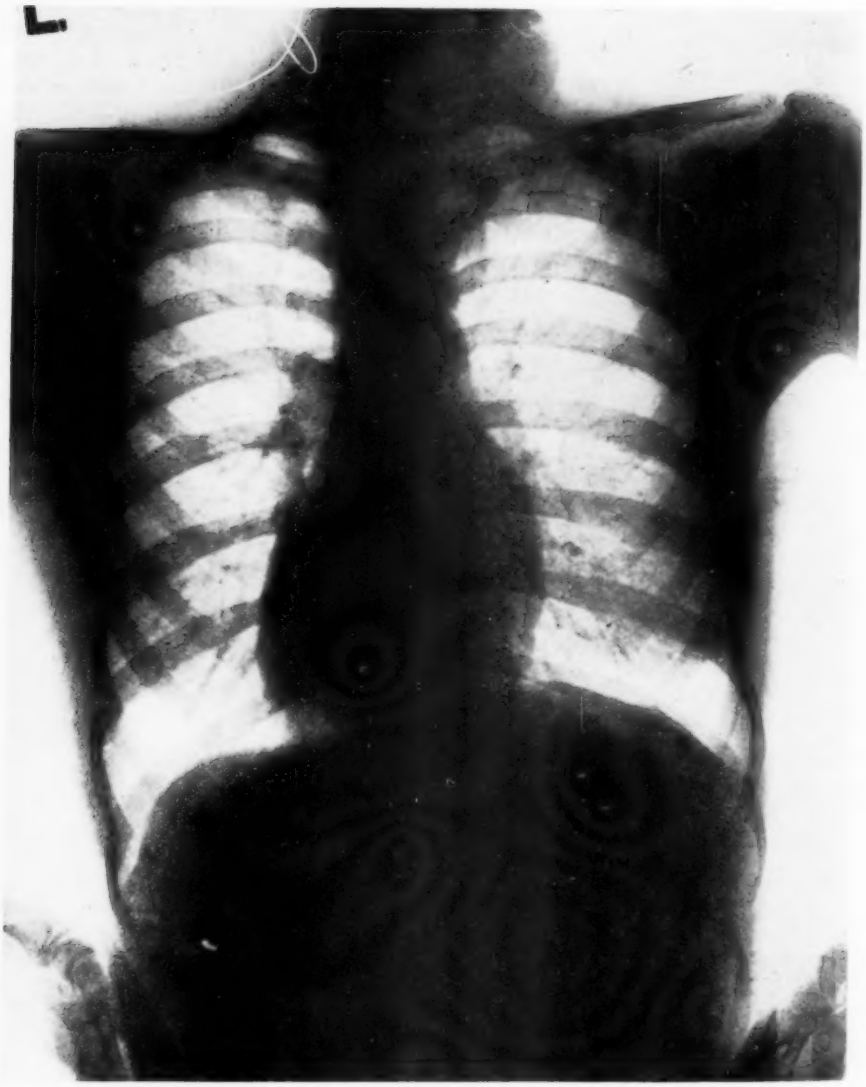
My colleague, Dr. Caulfeild[12], has been following one case with positive serological tests for 12 years in which at least two X-rays were negative until the last, when a clear cut minimal lesion was discovered in a practically symptomless man. This is the longest time taken by a contact-case to develop a lesion, where the history is known to any of us and the case under continuous observation.

Case 3. (Z) Fiancé classed as X-ray "C-R intermediate 2nd degree" with cough and expectoration March and April, 1926, then sent to sanatorium by me. Contact-case gave two 2nd class (positive) inhibi-



Serial serological graph of contact.

Case 2. (H.W.) showing positives in both tests.



CASE 5. Film 1 (M.N.E.) Jan., 1925. Three years after exposure. Lesion beginning in right apex.

tives and three two unit (positive) fixations in 4 double tests between September, 1926, and October, 1928. Two sets of stereos showed no lesion of parenchyma (Kruger). Contact-case seriously raised the question whether the alarm and restrictions were not worse than the possibility of the disease, wherewith I dropped the case.

Case 4. (R.E.) Exposed to sister, who was terminal case with positive sputum, and whom she nursed (both untrained) during the last 6 months of 1920; referred by Dr. W. R. Campbell. Stereograms of contact-case were clear (R4278, March, 1921, taken by Dr. H. M. Tovell and kindly procured from his file for me six years later). A short series of three tests were within normal limits and so after 18 months observation

CASE 5. Film 2 (M.N.E.), 1925. Flared into tuberculous lobar pneumonia four months later.

I discontinued, feeling further alarm unwarranted. She reported again, December, 1926, six years after exposure, having had 2 quarts of pleural effusion withdrawn, April of the same year (1926). Inhibitive now positive; steros (Dec., 1926, T.W.T. 26273 and Q.A. Sanatorium, 4776, Jan. 1927, kindly forwarded by Dr. P. M. Andrus) showed "several light but definitely floccu-lent shadows, peripheral zone, 1st and 2nd anterior interspaces and apices, both sides, less on the left, tuberculous (C-R minimal 1st degree). Referred to Dr. John Oille for consultation.

Case 5. (*M.N.E.*) This contact-case was exposed to gross and frequent doses; her father had active Tb., sputum positive, in the same house, 1922-23. Daughter-contact

CASE 6. Film 1 (Pete) Dec., 1925 (20987). Brother's chest two months after exposure ended.

was observed through 1924 but had no symptoms and no abnormal p.s. Then fixation was positive in January, 1925, and I found impaired resonance and shower of fine rales in right apex, whereupon I ordered X-ray for the first time. Minimal parenchymal lesion was demonstrated in R. apex, reproduced herewith. Sanatorium declined with a laugh, there being no symptoms. Four months later, acutely ill with high fever. Dr. L. J. Solway diagnosed tuberculous lobar pneumonia; X-ray reproduced herewith. Sputum loaded with tubercle bacilli.

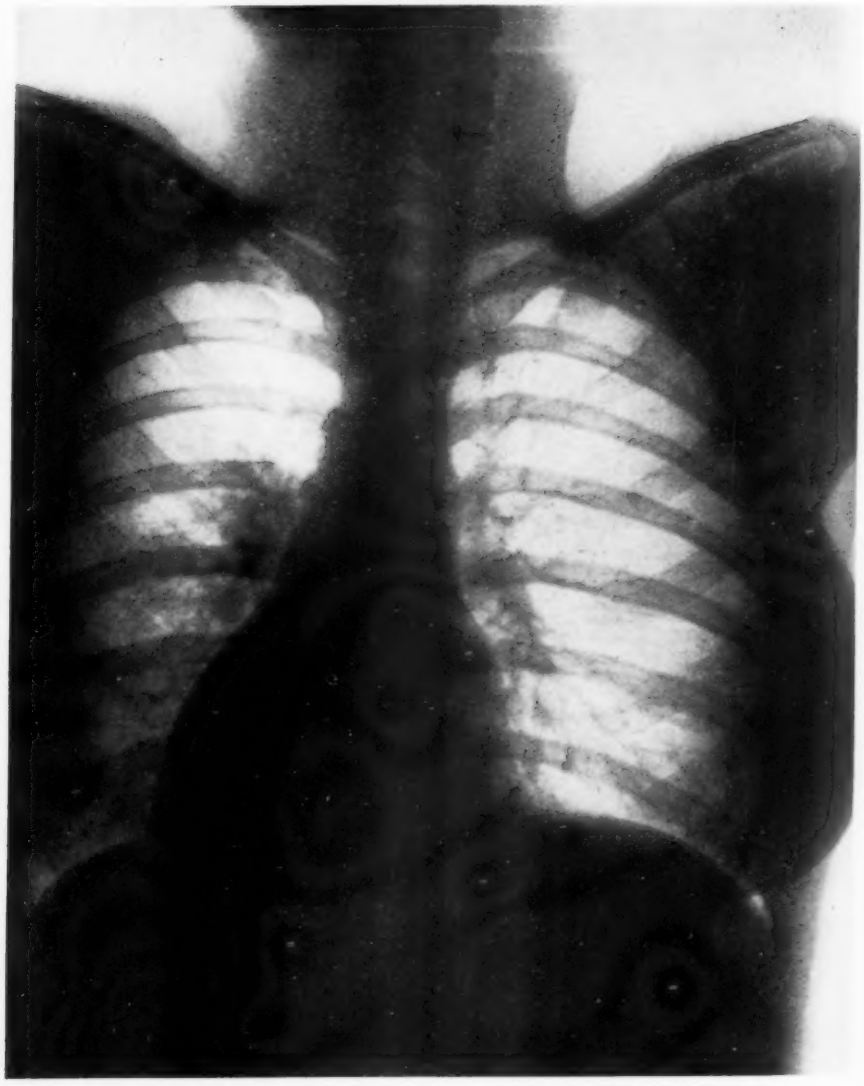
In relating the case at that time to Dr. Wm. Goldie and the late Prof. C. L. Starr, I had no X-ray corroboration of my negative clinical findings prior to

Lesion developing in brother twenty-seven months after tuberculous sister left for sanatorium.

CASE 6. Film 2 (Pete), Feb., 1928, (33367). Brother's chest over two years after exposure ended.

January, 1925, therefore no black and white proof that this date was the beginning of the lesion and the end of the incubation period. This decided me thereafter to order X-ray just within the 12 months after exposure, for two reasons: firstly, to have a picture of a clear chest for comparison in case a lesion or suspicion developed later, and secondly, to make certain that lesions were not developing earlier than I was looking for them, viz., 18 to 24 months. This rule I follow today in private and clinic practice.

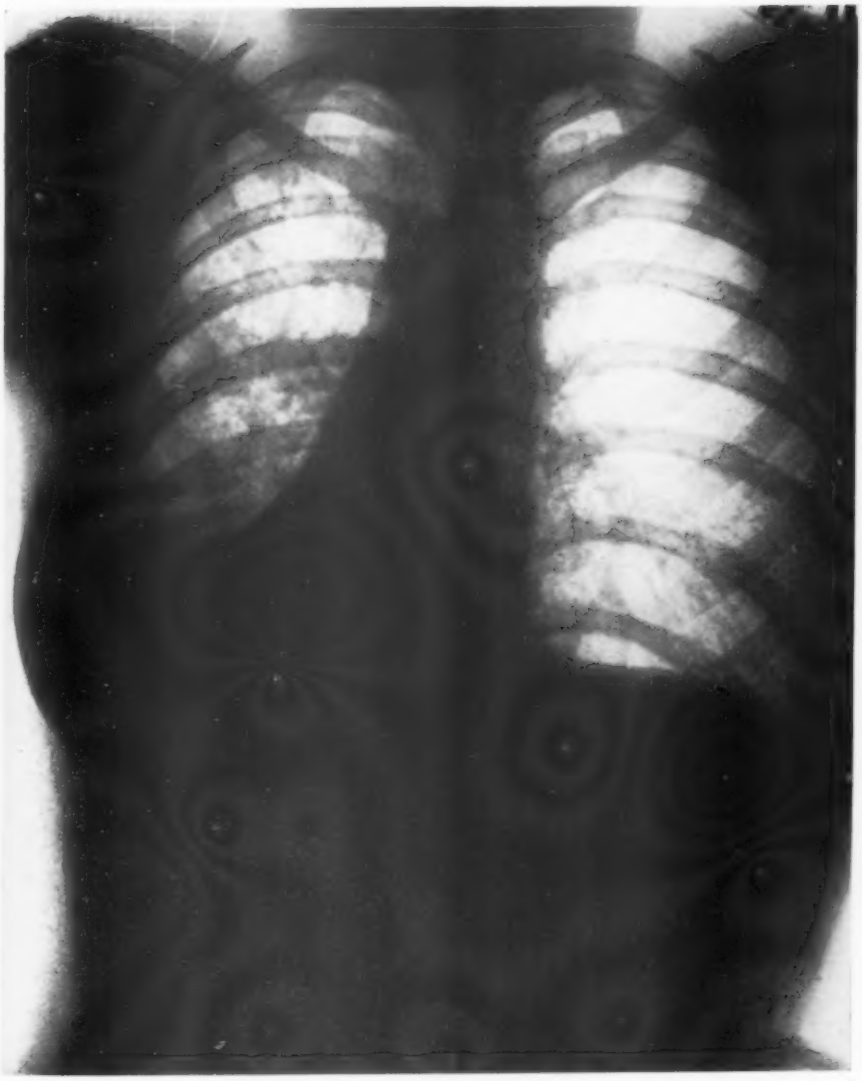
Case 6. (Pete—spoke little English) Was referred to T.W.H. chest clinic December,



CASE 8. Film 1 (F.D.) July, 1928. Twenty-five months after last intimate exposure.

1925, as contact by P.H. nurse because I had reported his sister tuberculous. He repeatedly denied living with, or going to see sister; he also reiterated that his sister had no cough. With this history of doubtful exposure, clear X-ray picture (20987 shown herewith), and serology negative three times, I discharged him October, 1926, as being not an actual contact. He reported again February, 1928, with symptoms, positive serology and positive sputum, definite X-ray lesion (33367 shown herewith), viz., "C-R intermediate, 1st degree". Sent to Mountain Sanatorium.

Again questioning the history concerning the possibility of exposure or actual contact, I received the same negative answers. Surely he was giving me wrong answers, or I was



Case 8. Film 2 (F.D.) Sept., 1928. Twenty-seven months after last intimate exposure Tuberculosis flaring in third year after exposure.

asking wrong questions! I changed my questions and received quite different answers:

Q. 1. "Had your sister a *hack?*"

A. 1. "Oh, yes, she had little hack, often, but no cough."

Q. 2. "Did your *sister go* to see *you?*"

A. 2. "Oh, yes, she came to my room three nights a week, eight to ten o'clock for three months, summer, 1925. She have no sitting room. I have."

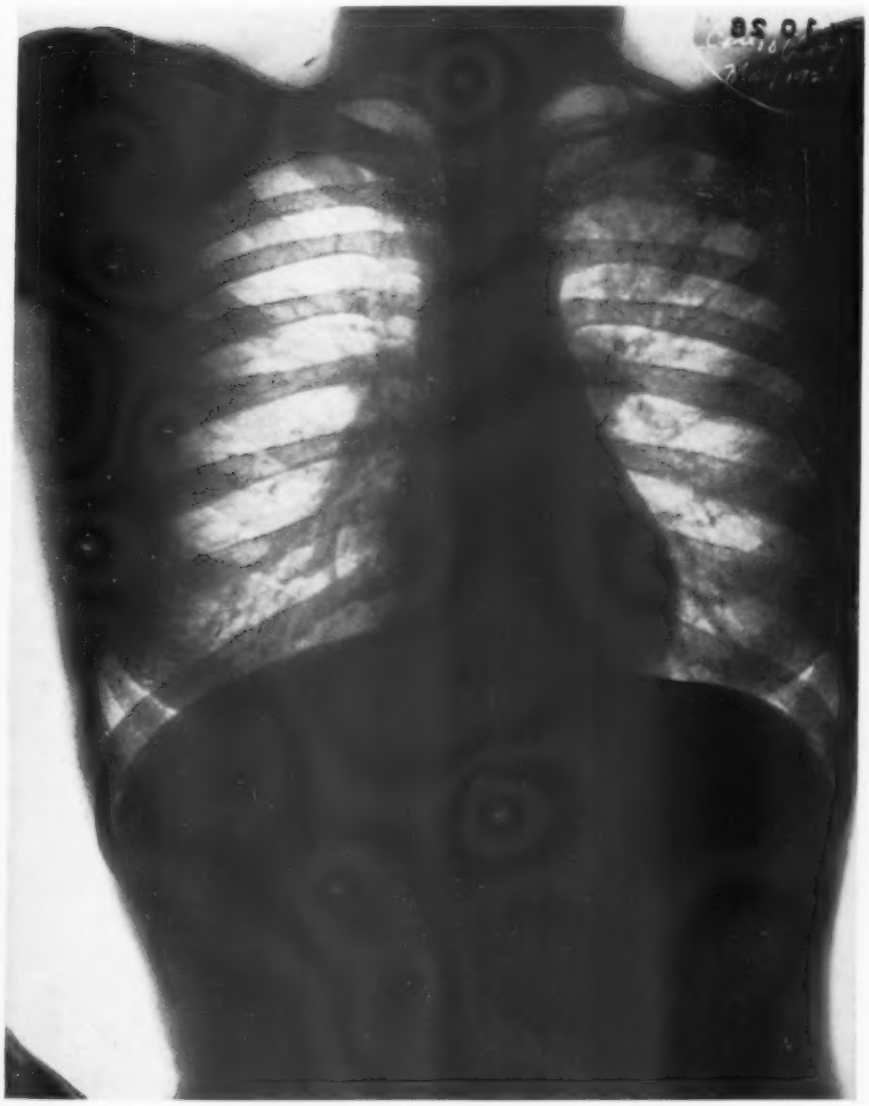
I felt like a fool.

Case 7. (M.E.) Was under observation because of frequent exposure in home of married sister with open Tb., 1920-22. During 1924 there was fatigue, 99.1°F. and slightly enlarged thyroid which were not explained by a single B.M.R. estimation

CASE 10. Film 1 (Lat.) Nov., 1925. Nine months after exposure ended.

A 2 unit (positive) fixation to tuberculo-antigens decided me (with some temerity) to send her to Freeport Sanatorium in June, 1924, although streos (T.W.H. 15278) showed clear lung fields. As visiting consultant to this institution, I was enabled to observe the case each month. In September, Dr. E. N. Coutts produced stereograms of a minimal parenchymal lesion half the width of a rib in diameter, (C-R minimal 1st degree) 2nd anterior interspace level, peripheral zone: almost as early as one could expect to catch a demonstrable lesion, particularly when watching for it.

Case 8. (F.D.) Lived with a sister who was an open case of Tb., January-June, 1926. She then entered training school for nurses. She was observed as a contact through 1927. X-ray clear in December and several blood tests within normal limits. Convinced as we were that this girl had been an *actual contact*, we were disappointed that certain



Demonstrating the shortest incubation period in our series observed by X-ray. CASE 10. Film 2 (Lat.) May, 1926. Fifteen months after exposure ended.

contingencies interfered with regular monthly serological tests[a]: we might have caught a biological reaction that would have warned us sooner of what was coming, that is, before it was too late. A second stereogram July 17, 1927, showed nothing definite (reproduced here) but inhibitive was positive, whereupon, Dr. George C. Anglin ordered her home to bed. Next month, while still in bed, there was troublesome spasmodic cough with expectoration and fever; not seen by physician. When I visited her, thirty miles away, the following month, September, I found profuse râles over left upper half, front and back not in themselves diagnostic of tuberculosis. Three sputum

examinations were negative, and I ordered her to town for X-ray September 28, 1928 (reproduced here). Tuberculous lesion shown throughout left upper. Tubercle bacilli found in sputum at Muskoka Hospital Feb. 13, 1929 (Reported by Dr. C. B. Ross).

We have too frequently seen that if a nurse breaks down with tuberculosis during training, the family blames the hospital and in particular the lady superintendent. The physician to training schools can no more suspect potential tuberculosis without history of contact than can he detect epilepsy by physical examination. I have therefore taken the stand that superintendents of training schools cannot afford to accept actual contacts as probationers, and in the autumn of 1928 I so advised Miss Beatrice Ellis, Toronto Western Hospital.

Case 9. (K) Consort was referred by Dr. Geo. S. Young, autumn 1925, for disposal, because of active Tb., and was sent to sanatorium for six months. In March, 1926, when the contact gave positive inhibitive but clear X-ray (5009 Richards), my request to report periodically was declined. Over two years later, in August, 1928, was twenty pounds heavier and symptomless when a free hemoptysis occurred. On auscultation I heard, following a cough at the end of forced expiration, a shower of râles over the right upper two spaces anteriorly, and stereograms (10202 Richards) showed a definite lesion in this area.

The only thing in addition which I might have done, was to have tried the effect of giving the contact one of my appointment cards to report for periodic observation—a system introduced and in common practice by a sister profession and accepted much more readily by the laity than is the case in medicine. They have their patients better trained than have we.

At this particular time another contact was under desultory observation, in fact apparently had stopped reporting. With the crash of case No. 9 more or less on my medical conscience, I decided to try the appointment card scheme, sending a letter with it. It resulted in only one more consultation: see case No. 3 (Z) above. (And both of these were active members of my own profession!)

Case 10. (Lat.) The husband was diagnosed tuberculosis throughout R. lung (C-R extensive 1st degree) February 1, 1925, and transferred to sanatorium until decease January, 1926. He had coughed since September, 1924. The wife-contact gave two units of complement fixed twice in 1925, stereos clear May, 1925, and again November, 1925, the latter (Kruger) reproduced herewith. Because of suspicious p.s., May, 1926, but with no complaints, Dr. Caulfeild referred her for stereogram, demonstrating lesion the size of tangerine (C-R minimal 2nd degree) in left upper, reproduced herewith. The incubation period was a minimum of 15 months; the exposure ended January 31, 1925. The remainder of the household were clear.

This fifteen months incubation period was the shortest in our series. The lesion might have been demonstrable by X-ray in twelve months; it certainly was not in nine and the contact was observed while she was under fairly strenuous working conditions.

Because of this revelation, if a contact is necessarily under similar social conditions, I feel safer in repeating stereograms every three months starting at twelve months after exposure.

Comment

Believing from observation that the tests were specific, these investigations commenced with an attempt to find

whether those recently in intimate contact with infective tuberculosis would react biologically, as indicated by the T.C.F. and the Inhibitive. The examples given go to show the value of the tests in contacts.

In attempting to classify some 200 contacts in private practice (and the same proportions would hold good in another 200 in clinic practice), there were four main groups.

Group I, the largest, were those who gave positive tests for two years or more and did not develop lesions.

Group II, the second largest, were those giving negative tests, also with no lesions.

Group III were those whom we did not see till two, three or four years after exposure; then, finding positive tests, we X-rayed and found lesions without apparent activity.

Group IV were those who developed lesions while under observation, always anticipated, (where closely followed) by positive tests.

The latter two groups, III and IV, were about equal in size.

It was thought that the findings in this ten year period were sufficient to stimulate the more active interest of others, even in face of the several difficulties mentioned.

It would seem that a provincial or state department of health may be willing to provide these tests, if we could guarantee equal use to urban and rural practitioners alike. For the latter however, time and transportation interfere; certain changes in the serum, too often occur, interfering with the reliability of the reactions. Dr. Arthur C. Norwich[15] of the D. P. and N. H. has recently made some modification of the technique with a view to eliminating possible false reactions.

In 1912 I "hoped that the closer investigation of *suspect* tuberculosis would soon be available for the many rather than for the few"[16]. Eight years later in 1920, although I did not anticipate Part II of the present paper on *contacts*, I did forecast[3] the name of Part I: "It is therefore satisfactory to have further definite assistance in diagnosis (by serology), even to the point of being able to recognize the disease in the *pre-clinical or biological* stage, and with this advance information, and by treatment, or restricted routine, to be able to keep the patient from reaching the stage of symptomatic tuberculosis."

Summary

1. Greater effort should be made, by more accurate history taking, to estimate the dose of tubercle bacilli received by contacts.

2. Some such classification as minimal, gross and massive contact, or casual, frequent and intimate exposure, is submitted.

3. Most "intimate" contacts have been found to react serologically for two years or more after the exposure.

4. A minority of adult contacts to open tuberculosis have been found to develop lesions when observed into the third or fifth year. The exact percentage is at present undetermined, and so far, has been difficult to estimate.

5. Contacts should be kept under observation for a longer period than was heretofore considered necessary.

6. Superintendents of training schools for nurses should not admit

recent intimate contacts as probationers.

7. Medical directors of insurance companies might well postpone insurance to recent contacts unless they have assurance of such financial standing and mental make-up as would guarantee against stress.

In addition to those mentioned in Part I, my appreciation is due Dr. G. C. Anglin and Dr. T. R. Welwood, my associates on the T.W.H. Chest Clinic for the past ten years, my confrère Dr. E. N. Coutts, Medical Superintendent, Freeport Sanatorium, and to the Board of Directors of the latter institution for their confidence and support since 1921 in the working out of some of these problems.

REFERENCES

[11]Ogden, W. E.: Title same as present paper, Part I, Ann. Int. Med., Vol. 4, No. 4, Oct., 1930, pp. 379-386.

[12]Caulfeild, A.H.W.: Personal communication to the author.

[13]Henry, Alfred: Diagnosis of Pulmonary Tuberculosis, Trans. Nat. Tb. Assoc., 1930.

[14]Caulfeild, A.H.W. and Richards, G. E.: The Systematic Study and Classification of Stereograms of the Chest, Can. Med. Assoc. Jr., 1927, Vol. XVII, pp. 794-797.

[15]Norwich, A. C.: Personal communication to the author.

[16]Ogden, W. E.: Factors Frequently Overlooked in the Early Diagnosis of Pulmonary Tuberculosis, Can. Med. Assoc. Jr., Vol. II, pp. 999-1009, Nov., 1912.

Some Observations as to the Results of Phrenic-Exeresis in Pulmonary Tuberculosis*

By Lieut. Colonel A. T. Cooper, M.C., *U. S. Army*

AVULSION of the phrenic nerve has been used as one of the agencies in collapse therapy for treatment of pulmonary tuberculosis at Fitzsimons General Hospital since approximately 1922.

Notwithstanding the fact that this operation has been of record in medical annals since 1913, the Staff at this Hospital, previously to 1922, felt some reluctance in recommending it, because the ultimate result as to the thinning and paralysis of the diaphragmatic muscles with the extent of the ascent of the upper abdominal viscera into the thoracic cavity, was unknown. It was feared with complete and permanent paralysis of a diaphragmatic leaflet, that a considerable eventration of the upper abdominal viscera might take place. By carefully watching, over a number of years, patients who have had this operation, it was shown that no marked eventration takes place, and the fact was demonstrated, that even in the permanently paralyzed diaphragm, a rise is not excessive and is limited.

There is one case, however, which would be well to mention at this point—where a patient having a large cavity in his left lung, refusing any operative procedure other than phrenic-exeresis, was eventually operated upon. During the progress of the disease, the whole of his left lung practically excavated. The left leaf of his diaphragm ascended about half way into the thorax, and along with this went the underlying viscera, that is, the stomach, and part of the colon. This man experienced rather disturbing gastro-intestinal symptoms, but eventually consented to a thoracoplasty on his left side. This is to be done in stages, so that the left side of his thorax is in the process of being totally collapsed, and he has since experienced a great deal of amelioration of his gastro-intestinal symptoms, which were not only incident to excessive cavitation in his left lung, but also were possibly due to the rather high position of his stomach and likely the colon.

As we have come to be more familiar with the results of this operation, we are becoming more liberal in recommending it, not only because of the ease and the lack of danger, which attends it—it can, in most cases be done under local anesthesia—but also because of the large per cent of patients, who in one way or another, derive considerable benefit from it. One

*From The Medical Service, Fitzsimons General Hospital, Denver, Colo.

benefit derived from this operation is that the work of the lung on the side on which operation was done, is lessened. This is demonstrated even in cases where there is no rise in the diaphragm by a definite lessening of the respiratory murmur over the base of the lung on the side operated upon. This phenomenon is more or less constant in all cases in which phrenic-exeresis has been done. Immediate result of the operation is, as a rule, a definite lessening of any pleuritic pains and discomfort which may have been present on the side from which the nerve has been avulsed. Slight discomfort may be complained of for a few days at the site of the operation and extending over the tract of the phrenic nerve, but this is minimal and of no consequence. After a few days, the patient generally definitely remarks that his cough is not so distressing, that although he may raise the same amount of sputum as he did prior to the operation, it is raised with less distress and effort. No comment on this phenomenon can be made with the data available. In a few days there is usually a noticeable rise apparent in the diaphragm on the side on which operation has been done, and this may increase up to a distance of six to seven centimeters in two or three weeks, or several months may elapse before the ultimate ascent has been reached.

The object of a phrenic nerve operation is to definitely lessen the aeration of the lung on the side operated upon, by paralyzing the corresponding half of the diaphragm. This paralysis, permitting the diaphragmatic leaflet to rise, partially compresses the lung. Therefore, phrenic-exeresis is one of the procedures to be used in collapse therapy. Some patients will accept this operation when they will accept no other form of collapse therapy.

If a complete avulsion is done, and 14 to 15 centimeters of the nerve removed, paralysis is usually complete. If but a small section of the nerve is cut out, the paralysis is only temporary. It has been reported that even in the avulsion of as much as 14 or 15 centimeters of the nerve, occasionally anomalous nerve branches have reestablished motor activity of the entire diaphragm.

The definite pumping, and possibly the tearing action of the diaphragm on pulmonary lesions in cavities in the lower part of the lung is considerably lessened by paralysis of this major muscle. We have found that even where there are extensive adhesions between the lung and the diaphragm, or between the visceral and parietal pleura in the lower part of the lung, an extensive rise of the diaphragm may result and be of benefit to cavities and lesions particularly in the central and lower part of the lung. This was definitely shown in one patient upon whom phrenic nerve operation had been performed with good results, and subsequently in order to completely collapse the cavity in the apex posteriorly, thoracoplasty was done. Several days after the latter operation, the patient died of embolism of the pulmonary vein of undetermined etiology. On post mortem examination it was found that even in spite of the extensive adhesions between the diaphragm and the lung pleura, and also laterally between the parietal and visceral pleura, an excellent rise had been obtained, the dia-

phragm having risen from six to seven centimeters.

It has also been noted that phrenic-exeresis may be of definite benefit in closing cavities and healing lesions not only generally throughout the lung, especially in the lower and central regions, but also occasionally in the upper portion as well. Even where there is considerable amount of uninvolved lung tissue between the diaphragm and a cavity in the upper part of the lung, following a phrenicectomy, the lower healthy lung seems not to be compressed so much as to rise with the diaphragm and to compress the more diseased upper portion of the lung.

The indications in general which are followed in this hospital in recommending a phrenic nerve operation are where the lesions show definite retrogression in one side, either with or without cavitation, and the lesions in the contralateral lung are minimal, with little or no cavitation present, pneumothorax being impracticable or having been tried unsuccessfully. However, it is difficult to find ideal cases, and if the internist delayed waiting only for ideal cases before making a recommendation for phrenic-exeresis, such recommendations would not be made in the majority of cases, and many patients who might derive a great deal of benefit from such an operation, would not be operated upon.

Phrenic-exeresis may be done as a sole procedure, but in most cases it is done in conjunction with other methods of collapse therapy. We have used it in conjunction with pneumothorax, as a preliminary step to thoracoplastic operations, and subsequent to thoracoplasties. Phrenic-exeresis is indicated and should be done on patients in whom pneumothorax being indicated, has been unsuccessfully attempted. It is both inadvisable and hazardous to attempt pneumothorax more than three or four times. With the presence of extensive pleuritic adhesions, there is always danger in attempting pneumothorax of producing air embolism which is a very serious complication. No more than three or four attempts at pneumothorax should be made, when, if unsuccessful, phrenic-exeresis should be seriously considered. Pulmonary lesions limited to the central or lower part of one lung are a definite and positive indication for phrenic-exeresis. Most of such cases received marked benefit not only in their symptoms but also in providing a permanent collapse therapy to diseased pulmonary areas. Painful and persistent pleurisy in the lower part of the lung, with hiccough or pleuritic pain, is also an indication for phrenic nerve operation. Pleuritic pain is lessened in patients with such complications after operation.

Preliminary to thoracoplasty—where a complete collapse of one lung is desired and several stages of thoracoplasty are contemplated, phrenic-exeresis may be done, as this will in many cases, lessen the number of ribs which it is necessary to resect in order to obtain a complete collapse, and so produce less thoracic deformity. Where a complete thoracoplasty is not contemplated, in many cases phrenic-exeresis is advisable in order to partially collapse the lung on the side to be operated on, as a preliminary measure and to test out the opposite lung. Such a test will often give the clinician an

idea as to how well the contralateral or minimal involved lung is going to react to a thoracoplastic operation on the most diseased side. In all probability phrenic-exeresis is of value in possibly preventing paradoxical or pendulum breathing subsequent to thoracoplastic operations. This complication is a decidedly serious one following operations on the chest, and phrenicectomy may be of help in preventing it.

The contraindications are of course extensive—bilateral pulmonary disease particularly, where there is rather extensive bilateral cavitation, although we have not hesitated even in terminal cases with distressing cough and pain on the most involved side due to pleurisy, to recommend phrenicectomy, where chest pain can possibly be lessened, and where it is thought that the patient would be made more comfortable by lessening his distressing cough and enabling him to eject his sputum with less effort.

Cases with marked bilateral emphysema or asthma are not good cases for phrenic-exeresis. In miliary tuberculosis, extensive throughout both lungs, of course no benefit can be obtained. Cardiac and renal diseases are not considered contraindications, if not advanced.

Since 1922, this operation has been performed on approximately two hundred patients at this hospital, and in studying a portion of these patients, it was found that approximately 70% of those operated on the right side showed definite rise, while on the other hand only 55% of those who were operated on the left side, showed definite rise. This observation was made after careful comparison of preliminary X-rays and plates following operation, and shows that there are greater chances of a more successful result following operation on the right side than on the left, if success is to be measured by a rise in the diaphragm. Yet we have found that a rise in the diaphragm is not the sole criterion for successful results. Many patients, who showed no rise, yet as a result of diaphragmatic paralysis as shown by fluoroscopic examination of the diaphragmatic leaflet, showed definite improvement as far as tending to clear up the pulmonary lesions was concerned, and this is to be explained only as a result of a definitely paralyzed diaphragm which lessened pulmonary ventilation and action, as there was no apparent resultant vertical compression of the lung.

The question of gastrointestinal disturbances following exeresis has been raised, and while there are approximately 40% of the cases who have symptoms, from slight to rather marked, persisting for two or three weeks, these symptoms have not been such as to interfere with their digestion, and have subsided after a few weeks time.

It may be well finally to mention an unfavorable termination in a case of pulmonary tuberculosis on which a left phrenic-exeresis was done, because it was thought that a midlung cavity was present on that side, but which eventually was determined to be a localized spontaneous pneumothorax. A good rise of the left diaphragm resulted. Subsequently, due to a large apical cavity on the right, an upper stage thoracoplasty was recommended and done on this side. Immediately upon

completion of the thoracoplasty, the patient developed paradoxical respiration and died shortly. From this one case, it would appear that thoracoplasty is a hazardous procedure, if phrenic-exeresis has been done on the opposite side.

In studying the effects on cavities, it has been noted that cavities in the midlung or base, are more apt to be benefited by a phrenic-exeresis than are cavities higher in the lung or in the apex. A tendency toward compression has been noted in about 42% of the cavities in the midlung or base, while only 30% of the cavities higher in the lung than the central part have been noted to be definitely benefited.

The same is true of involvement in different parts of the lung, even without cavitation. It is well to remark here that phrenic-exeresis is not a panacea, even for basal cavities or basal involvement, as we have noted in one case having a cavity low in the base of one lung on which phrenic nerve operation was performed, that no benefit was derived from the operation, the cavity continuing to enlarge, notwithstanding a definite rise in the diaphragm.

SUMMARY

I. Phrenic-exeresis is of value in many cases of pulmonary tuberculosis where the lesions are mainly unilateral.

II. Beneficial results have been noted even where there is no corresponding rise in the diaphragm.

III. A good rise of the diaphragm may ensue even with the presence of adhesions.

IV. Phrenic-exeresis is particularly indicated in unilateral cavitation involving the lower or central part of one lung.

V. Phrenic-exeresis is indicated where attempt at inducing pneumothorax is unsuccessful.

VI. Phrenic-exeresis is useful as a preliminary step where complete thoracoplasty is contemplated, as sufficient collapse may be obtained with resection of fewer ribs and less deformity; also it is useful as a preliminary procedure in many cases to test out the contralateral lung.

VII. This operation frequently ameliorates much of the distressing and wracking cough present in far advanced cases and enables the sputum to be raised with less effort.

Primary Tuberculosis of the Spleen: Its Clinical Resemblance to Banti's Disease.

With a Report of Three Cases*

By Alvin E. Price and Ronald L. Jardine, *Detroit*

SECONDARY involvement of the spleen in cases of generalized tuberculosis is not rare. Griffin[1] has estimated its occurrence in twenty per cent of adults, while in children he regards it about three times more frequent (50-66 per cent). Others would place these figures still higher, regarding the incidence close to one hundred per cent. "Primary Tuberculosis of the Spleen" on the other hand, as described by Auché[2], Bayer[3], Block[4], Ciacco[5], Léon-Kindberg[6], Quéne and Baudet[7], Sotti[8] and others, is found to be much less common. Winternitz[10] in 1912 reviewed some fifty-one cases reported up to that time and since then about half again as many have been reported.

By the term "Primary Tuberculosis of the Spleen" is implied the localization of the process in this organ to an extent which is greater than that found in any other part of the body. It does not necessarily mean, that the spleen is the portal of entry of the infecting organism, nor does it preclude the existence of others tuberculous foci in the body (Klotz[9]).

During the past year we have had the opportunity to study three cases which have come under observation in Harper Hospital. In all three a pre-operative diagnosis of Banti's disease was made, and it was not until subsequent laparotomy with microscopical study that the tuberculous nature of the condition was recognized. In view of the mistaken diagnosis in all three cases, we became impressed with the clinical similarity existing between primary tuberculosis of the spleen and Banti's disease, and concluded that it would be of interest to report the cases from this standpoint.

Case 1. *History.* A. P., adult male, age 41, was admitted to the medical service of Harper Hospital on April 15, 1920. His illness started about six months prior to his admission with generalized weakness and pain in the U.L.Q. Somewhat later he had profuse night sweats. The physician consulted at that time instituted a course of X-ray treatments over the spleen, this resulting in some improvement in the patient's general condition. Several months later, however, the weakness returned and the patient was admitted to a local hospital. At this time the spleen and liver were both found to be enlarged, the former extending to the iliac crest, and the latter to ten centimeters below the costal margin. The blood picture was as follows—Hemoglobin, 42%;

*From Harper Hospital, Detroit, Michigan.

R.B.C., 2,250,0000; W.B.C., 1950. P.M.N., 26%. S. L. 18%. Eos. 2% and Myelocytes 54%. A diagnosis of chronic myelogenous leukemia with marked anemia and leukopenia (secondary to X-ray therapy) was made, and a series of eight blood transfusions was given. Following the latter, the hemoglobin became 60%, the red count rose to 3,200,000 and the white count increased to 7,100. All myelocytes disappeared from the blood stream. The general condition of the patient then improved, although no difference was noted in the size of either the liver or the spleen. Shortly after his discharge from the above institution he was admitted to our hospital, his chief complaints being "weakness and a mass in the abdomen."

The family and past medical history were negative.

Physical Examination. The patient was moderately well developed and poorly nourished having a peculiar "muddy" tint to the skin. The eyes were somewhat sunken in their orbits. The mucous membranes of the mouth were pale, without pigmentation. The chest was symmetrical with definite depression of the supra- and infraclavicular fossae. Resonance was impaired high in the left axilla. Breath sounds were exaggerated over both upper lung fields and a few fine crepitant râles were heard over the left base posteriorly. Heart was negative except for a systolic murmur at the apex. B.P. 90/50. Abdomen—rotund and tense with evidence of fluid. The spleen extended well below the umbilicus and medially as far as the mid-line. The surface was hard and slightly irregular on palpation. The liver extended two finger breadths below the costal margin. Extremities—negative.

Laboratory Data. Blood Count (4/22/29) HB. 70%. R.B.C. 3,680,000. W.B.C. 6,000. P.M.N. 85%. S.L. 11%, L.L. 4%. Red cells showed some poikilocytosis. Reticulated cell count .7%. Platelet count 650,0000. Bleeding time 2 mins. Coagulation time 4½ mins. Blood Wassermann and blood sugar—normal. Blood nitrogen 40 mgs. per 100 c. c. Urinalysis—negative except for urobilinogen.

Liver function test—Van den Bergh reaction—direct—neg.; indirect—weakly positive. Icteric index 4. Bromsulphalein dye test—negative. Levulose tolerance test—negative.

X-Ray—Lungs—negative for evidence of tuberculosis.

Clinical Course. While in the Hospital, the patient complained of weakness and abdominal discomfort,—the latter due to pressure from the enlarged spleen. The temperature varied between 100.4 and 101.6; the pulse between 80 and 120. On the basis of the above findings, a clinical diagnosis of Banti's disease was made and splenectomy decided upon. At the operation the spleen was found to be enormously enlarged and adherent to all the surrounding structures by easily separable adhesions. The neighboring tissues showed signs of acute inflammation. Free fluid was found in the abdomen and the liver was slightly enlarged.

On the day following the operation, the temperature rose to 102, the pulse to 140, and the patient expired. Permission for autopsy could not be obtained.

Pathological Report. Spleen measured 30 cm. in its longest diameter and showed numerous large wedge-shaped areas of caseation necrosis on its surface and on cut section. (Figure 1). Microscopic examination revealed marked thickening of the splenic capsule. Throughout the pulp were myriads of miliary tubercles in various stages of development,—some already undergoing caseation. Farther removed from the capsule were large caseous areas surrounded by avascular epithelioid zones with many multinucleated giant cells. (Figure 2).

Pathological Diagnosis. Active Chronic Tuberculosis of the Spleen.

Case 2. History. D. H., white female, age 41, was admitted to Harper Hospital Nov. 16, 1929, complaining of weakness and a mass in the upper part of the abdomen. In 1919, when the tumor was first discovered, the patient was submitted to an exploratory laparotomy, after which she was told that she had an "enlarged spleen and a large fibrous liver". During the following year, a course of X-Ray treatments was instituted but without apparent effect on the size of either the spleen or liver. The general condition of the patient remained unchanged until April, 1929, (seven months prior to her

admission to our hospital), when she started to lose weight, became weak and had frequent night sweats. There was also an occasional afternoon fever, but no cough.

Physical Examination. The patient was well developed but poorly nourished, having a definite pallor combined with a faint icteric color to the skin. Eyes—negative except for slight icterus of sclerae. Lungs—negative for evidence of tuberculosis or other pulmonary disease. Heart—negative. B.P. 108/68. Abdomen—There was a large, smooth and slightly tender mass in the U.L.Q.—extending to within 2.5 cm. of the iliac crest and well over the midline. Liver was enlarged to five finger breadths below the costal margin. The surface was smooth and firm. No ascites was demonstrable. Extremities—negative except for slight tenderness over right tibia.

Laboratory Data. Blood Count (11/16/29): Hb., 60%. R.B.C., 3,360,000; W.B.C., 2,950; P.M.N., 48%; L., 43%; M., 2%; Eos., 7%. Blood Wassermann—4 plus. Blood N.C.N., 26 mgm. Blood Sugar, .087 mgm. Blood fragility—beginning hemolysis .45%. Complete hemolysis, .35%.

Urine—negative. No urobilinogen.

Van den Bergs—direct—slightly positive; indirect—positive.

X-Ray of chest revealed an increase in lung markings in left base, but no definite parenchymal lesions.

Clinical Course. During her stay in the hospital, the patient had a daily afternoon temperature elevation of 100°. On the third day one X-Ray treatment was given over the spleen. Two days later, a direct blood transfusion (300 c.c.) was done, followed in two hours by splenectomy. The preoperative diagnosis was Banti's disease.

At operation, the spleen was found to be hard in consistency and about six times its normal size. The liver was also markedly enlarged. No free fluid was seen in the abdomen.

FIG. 1. Spleen showing wedge-shaped area of caseation necrosis on cut section.

On the third day post-operative, the patient died. Permission for autopsy could not be obtained.

Pathological Report. Spleen was enormously enlarged and firm in consistency. On the anterior surface, there was a large area of caseation necrosis. (Figure 3). Microscopic examination revealed large areas of caseation surrounded by an avascular epithelioid zone. There were very few giant cells. Recent disseminating miliary tubercles were found throughout the splenic pulp in the zone outside of the caseous areas. (Figure 4).

Pathological Diagnosis. Chronic caseating tuberculosis of the spleen with recent dissemination.

Case 3. *History.* G. A., white female, age 33 yrs., was admitted to Harper Hospital Aug. 8, 1929, complaining of weakness, tumor in the abdomen and a loss of nine pounds in weight. The abdominal tumor had been noticed for the first time about one year previously, and since that time had increased in size gradually. There was no history of fever, night sweats, cough, jaundice or hematemesis. Amenorrhea had been present for six months.

Physical Examination. The patient was poorly nourished and poorly developed with evidence of recent loss of weight. Eyes—no icterus of sclerae. Lungs—breath sounds bronchovesicular in type with fine râles at both apices. Heart—negative. B.P., 120/75. Abdomen—there was a large, freely movable mass in the U.L.Q., extending to the iliac crest below and to the midline medially. Surface was smooth and firm. Liver—not demonstrably enlarged. There was moderate ascites. Extremities—negative.

Laboratory Data. Blood Count (8/8/29): Hb., 70%; R.B.C., 4,420,000; W.B.C.,

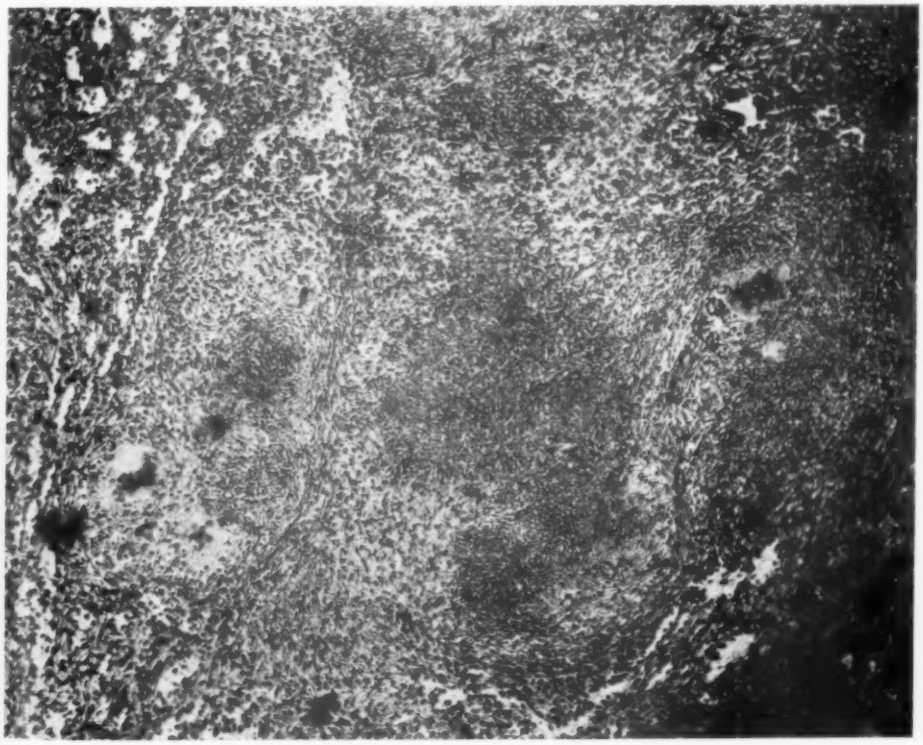


FIG. 2. Photomicrograph of Figure 1, showing giant cells and extensive caseation necrosis.

3,600; P.M.N., 81%; L., 18; M., 1. Clotting time—4 min. Blood N.C.N. 25 mgm. Blood Wassermann negative. Urine negative.

Clinical Course. The patient had a daily afternoon temperature elevation of from 100° to 102°. Five days after admission she was submitted to operation (splenectomy) with a clinical diagnosis of Banti's disease. The spleen was found to be markedly enlarged, the liver slightly so. Moderate ascites was present. There was no evidence of intra-peritoneal tuberculosis.

Following the operation, the patient made an uneventful recovery, and was discharged two weeks later.

Pathological Report. The spleen was of firm consistency, weighing 2200 grams, and measuring 25 cm. in its longest diameter. (Figure 5). Microscopic examination revealed a diffuse distribution of confluent tubercles. The tubercles in general were small, consisting of avascular epithelioid whorls with large multinuclear giant cells. In addition there was a diffuse fibrosis of the splenic pulp with large areas of caseation due to breaking down of tuberculous masses. A few myeloid areas were distributed through the splenic pulp. (Figure 6).

Pathological Diagnosis. Chronic tuberculosis of the spleen with recent dissemination.

Discussion

An analysis of the above three cases of primary tuberculosis of the spleen from the standpoint of their clinical resemblance to Banti's disease, reveals several features which are of particular significance. In the first place, the age incidence is similar in both conditions. In his discussion on Banti's disease, Osler[12] states that "it is a disease of young and middle life, the majority of

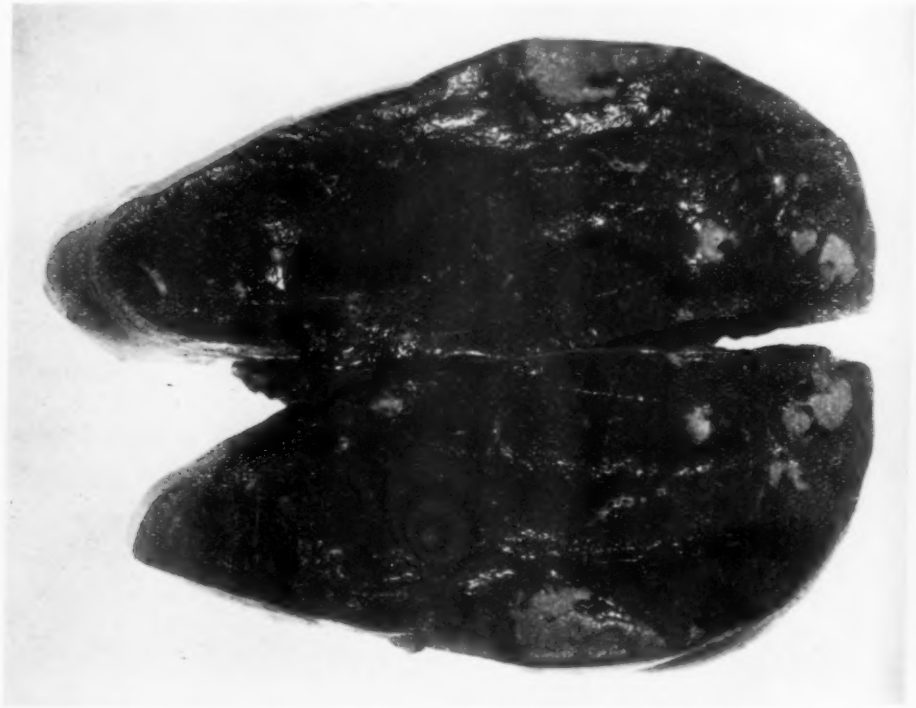


Fig. 3. Cut section of spleen showing area of caseation necrosis at periphery.

cases occurring before the fortieth year." In the cases reviewed by Winternitz[10], fifty per cent occurred between the ages of twenty and forty. In our cases, the maximum age was forty-one. A second feature of even greater significance is the associated splenomegaly and liver enlargement. While a well established combination in most cases of Banti's disease, its occurrence in tuberculosis of the spleen is probably less frequent. In the literature one finds reference made to this in various case reports, notably those of Drebschok[13] and also of Palumbo[14]. Indeed, the latter would consider tuberculosis of the spleen with associated liver enlargement as a distinct group. The degree of splenomegaly has varied considerably—the spleen in Giffin's[1] case weighing more than five hundred grams (508 gm.) while in Hallermann's[15] case it exceeded two kilograms (2850 gm.). The hepatic enlargement has been equally variable. Pathologically, while some similarity to Banti's disease was noted in one case (Tapie[16]) the morbid anatomy in splenic tuberculosis has been of several types. Thus a miliary form has been described by Bufalini[11] and more recently by Moses[17]. Tuberculous cysts of the spleen have been reported by Hayden[18], and also by Peck[19], while a third type was described by Coyon, Clog and Brun[20] in which large areas of necrosis were scattered

FIG. 4. Photomicrograph of Figure 3, showing tubercles with giant cells and adjacent epithelioid zone.

throughout the splenic tissue. The first and to a lesser extent the second of our three cases belong to the latter class.

Ascites, often seen in cases of Banti's disease in the terminal stages, has also been noted in tuberculosis of the spleen. In the case described by Palumbo[14], the ascites was associated with a "chylothorax". In our series, free peritoneal fluid was present in two cases (Cases 1 and 3).

The blood picture has been of interest because of its diverse manifestations. Winternitz[10] found a normal blood count in thirty-four, an anemia in forty-two and polycythemia in twenty-three per cent of cases. Other cases showing a polycythemia have been reported by Rendu and Widal[21], Coyon, Clog and Brun[20], and also by Head[22]. An anemia with an associated leukopenia, not unlike that frequently seen in Banti's disease, has been noted by Drebschok[13], Giffin[1] and Hallermann[15]. Cases 1 and 2 in our series belong to this group. On the other hand, the relative polynucleosis in the first and third of our cases stands in contrast to the lymphocytosis usually seen in Banti's disease. Still another type is found in those cases having a leukemic blood picture. Hallermann[15], in 1927, reported a case having a preoperative diagnosis of aleukemic leukemia, with a total white count of 4,300 and eighty-three per cent lymphocytes. Giffin[1], several years earlier, reported a case of miliary tuberculosis of the spleen having a blood picture which was typical of myelogenous

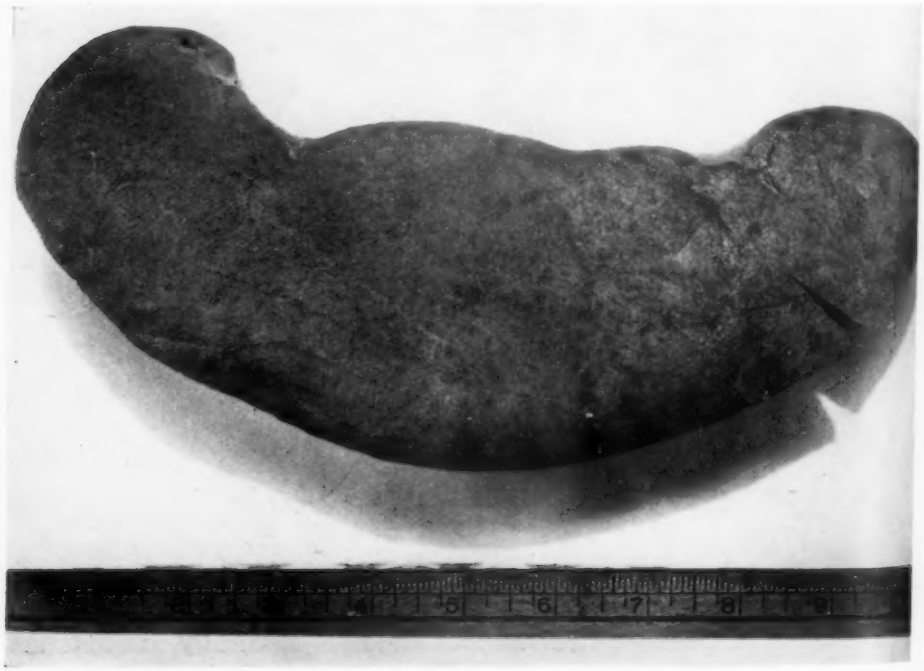


FIG. 5. Longitudinal section of spleen.

leukemia, and a second one having the characteristics of an aplastic anemia. It is interesting to note in this connection that Case 1 in this paper was originally diagnosed "myelogenous leukemia" because of the large number of myelocytes in the blood stream.

There is no characteristic symptomatology which would aid one in distinguishing primary tuberculosis of the spleen from other types of splenomegaly. The upper left quadrant tumor with the accompanying weakness, pain and resulting pressure symptoms might be found in almost any splenic disease, and although several diagnostic procedures have been suggested by different writers, viz; tuberculin reaction (Bayer[3], Bufalini[11]) splenic puncture, etc., it is only by microscopic study of the splenic tissue after laparotomy, that the diagnosis can be established with certainty. Special mention, however, should be made of fever as a diagnostic criterion, because on several occasions this has been offered as the differentiating factor. While one finds it recorded in many cases of splenic tuberculosis, it is only rarely seen in Banti's disease. An afebrile course, on the other hand, should not rule out the former. Thus Bayer[3] states that it may exist with or without fever, while Magnac[23] reports a case with a normal temperature. In the series reviewed by Winternitz[10],

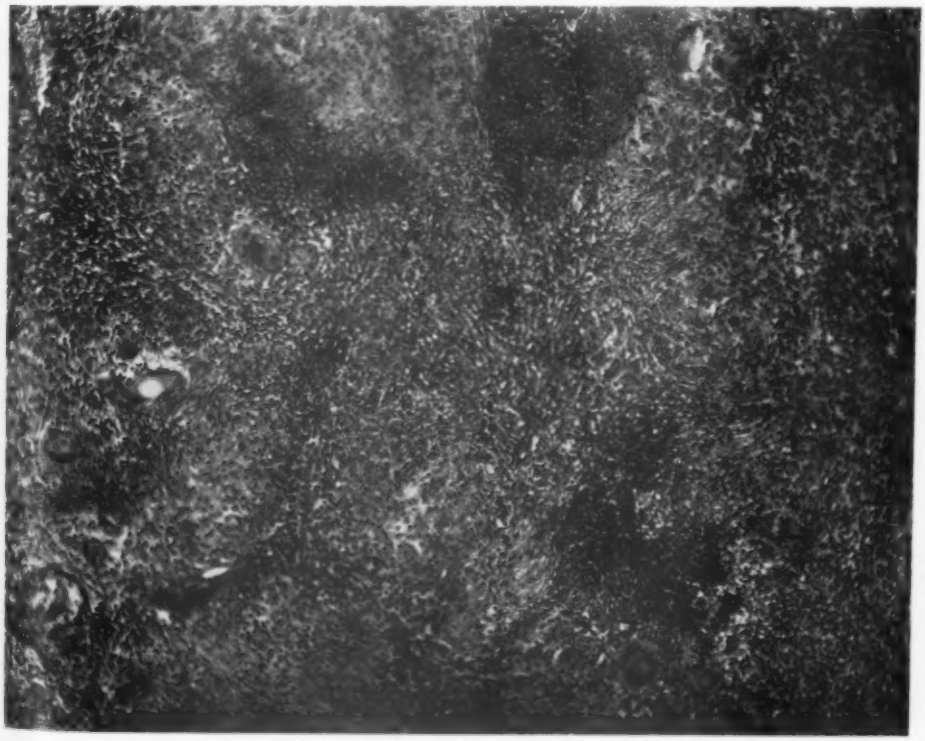


FIG. 6. Photomicrograph of Figure 5, showing diffuse fibrosis of splenic pulp and many giant cells.

twenty-one percent had normal temperatures. Some degree of fever was present in all of our cases.

The treatment of tuberculosis of the spleen, like that of Banti's disease, is surgical—i.e. splenectomy. This has been discussed quite at length by Linder[24], Delore[25], Villard and Santay[26], Carling and Hicks[27], and others. Fraske[28] reports the results of splenectomy in ten cases which were operated upon from a series of twenty-nine. Seven recovered. Roentgenotherapy has also been advocated. In the reported by Hallermann[15], X-Ray was used with apparent success for four years, but at the end of that time the original symptomatology returned.

A review of the literature reveals comparatively few instances in which the clinical similarity between tuberculosis of the spleen and Banti's disease is discussed. Thus in 1927, Sartorari[29] described the case of a man, 46 years of age, whose symptomatology consisted of general debility, pain in the left upper quadrant, fever and night sweats. Physical examination showed the patient to be anemic with an enormous enlargement of the spleen and a moderately enlarged liver. Lungs and sputum were negative. The blood picture showed a secondary anemia, with a white count of 4,000 and the following differential: P., 63%; L., 21%; M., 17%. A subsequent blood count made ten days later showed a definite lymphocytosis of 71%. A preoperative diagnosis of Banti's disease was made and splenectomy performed. Five days after operation, the patient died, the spleen showing diffusely disseminated tubercles with some caseation. The liver also showed numerous tubercles. A second case which came to operation with a preoperative diagnosis of "Banti's disease" was reported by Bufalini[11].

Summary and Conclusions

Three cases of primary turerculosis of the spleen are reported and one case from the literature is reviewed. In all four, a close similarity to Banti's disease was noted. The resemblance between the two conditions was based not only upon the general symptomatology, such as pain and tumor in the upper left quadrant, weakness, etc., but also upon definite physical and laboratory findings, viz.—an associated liver enlargement, ascites and blood picture.

Special attention is called to the fact that fever, while usually present in tuberculosis of the spleen, is not an invariable accompaniment, and hence its absence should not rule out this condition.

The pathology of splenic tuberculosis is discussed and its variability noted.

The treatment, by almost unanimous agreement, is surgical, i.e., splenectomy.

References

[1]Giffin, H. Z.: Tuberculosis of the Spleen. Med. Clinics N. A. 3:765-771, Nov., 1919.

[2]Auché, B.: Tuberculose primitive de la rate. Journal de Méd. de Bordeaux, XXXI; 381-384, 1901.

[3]Bayer, J.: Über die primäre Tuberculose der Milz. Zentralblatt für innere Medizin, XXVI; 1062-1063, 1905.

[4]Bloch, R.: Contribution à l 'étude anatomo-clinique de la tuberculose primitive de la rate. Rev. internat. de la tuberc., Par., XII; 23-32, 1907.

[5]Ciaccio, C.: Primäre tuberkulose Splenomegalie. Deutsche. Ztschr. f. Chir., Leipz., XCVIII:464-473. 1909.

[6]Léon-Kindberg, M.: La tuberculose primitive de la rate. Rev. Méd.-chir. d. mal du foie. II: 131-144, Mar., Apr., 1927.

[7]Quéné, E. and Baudet, R.: La tuberculose primitive de la rate. Rev. de Gynéc. et de chir. abd., Paris, XI:317-352, 1898.

[8]Sotti, G.: Della tubercolosi primitiva della milza. Arch. per le sc. med., Torino, XXXII:238-271, 1908.

[9]Klotz, O.: Obsolete Miliary Tubercles of the Spleen. Am. J. Med. Sc. 153-786, June, 1917.

[10]Winternitz, M. C.: Tuberculosis of the Spleen. Arch. Int. Med. IX: 680-697, June, 1912.

[11]Bufalini, M.: Splenomegalia tubercolare primitiva a forma miliarica (intervento operativo reporto istologico). Riforma med., Napoli, 37:434-438. May 7, 1921.

[12]Osler, W.: Principles and Practice of Medicine, 912-915.

[13]Drebschok, F.: Eine Fall von gross knotigen Milztuberkulose mit Hirntuberkeln. Wien. klin. Wchnschr. 34:603-604, Dec. 15, 1921.

[14]Palumbo, G.: Un caso di tubercolosi primaria della milza con ascite chilosa e chilotorace. Il Policlinico Med. 11: 561-570, 1904.

[15]Hallermann, A.: Über den Verlauf eines Falles von Milztuberkulose und seine Behandlung mit Röntgenstrahlen. Klin. Wchnschr, 6:502-503, Mar. 12, 1927.

[16]Tapie, J.: Splénomégalie tuberculeuse a évolution fibreuse. Bull. et mém. Soc. méd. h. hôp de Paris 50:1510-1514, Nov. 4, 1926.

[17]Moses, H. M.: Miliary Tuberculosis of the Spleen. Long Island M. J., Brooklyn, XIX:139-142 (1925).

[18]Hayden, A. M.: A case of tuberculosis of spleen with surgical treatment. Tr. Indiana M. Soc., Indianap., 1897:96-106.

[19]Peck, C. H.: Tuberculous Cyst of Spleen; Splenectomy; Recovery. Surg., Gyn. and Obst., 39:162-164, Aug., 1924.

[20]Coyon, A., Clog, W., Brun, M. C.: Sur un cas de tuberculose de la rate accompagnée de polycythémie. Bull. et mém. Soc. méd. d. hôp. de Paris 51; 48-53., Jan., 1927.

[21]Rendu and Widal: Splenomégalie tuberculeuse sans leucémie avec hyperglobulie et cyanose. Bull. et mém. Soc. méd. d. hôp. de Paris 16: 528-541, (1899).

[22]Head, G. D.: Tuberculosis of Spleen with Polycythemia and Splenomegaly Improved by Treatment with Radium and Benzene. J.A.M.A. 83:40-41, July 5, 1924.

[23]Magnac, J. L.: Surgical Tuberculosis of Spleen, with the report of a case. Internat. Clinics 1:106-119, Mar., 1924.

[24]Linder, W.: Splenectomy for Tuberculosis of Spleen. Long Island M. J. Brooklyn, 10:320-322, 1916.

[25]Delore, X.: Splénomégalie tuberculeuse; splénectomie. Lyon Médical 107:510-513, (1906).

[26]Villard and Santy: Splénectomie pour tuberculose massive de la rate. Lyon méd. 120: 151-155, (1913).

[27]Carling, E. R., and Hicks, J. A. B.: Two Cases of Tuberculous Splenomegaly. Brit. M. J. 2: 291-292, Aug. 15, 1925.

[28]Franke, F.: Ueber die primäre Tuberculose der Milz. Deutsche. med. Wchnschr., Leipz. u. Berl., 32: 1656-1659, 1906.

[29]Sartorari, F.: Sulla tuberculosi primitiva della milza. Arch. di pat. e cl'n. med. 6:137-148, Mar., 1927.

Superior Longitudinal Sinus Thrombosis With Subarachnoid Hemorrhage

Report of a Case*

By Roy S. Leadingham, M. D., F.A.C.P., *Atlanta, Ga.*

SUBARACHNOID hemorrhage may be the primary cause of death following injury to the head, or may result from a variety of intracranial vascular lesions. Smith[1] lists as the most common causes, aside from trauma: cerebral aneurysm, toxic infectious diseases, cerebral neoplasms, and hemorrhagic diseases. Neal[2], reviewing thirty-five cases, gives the following causes:—

Head Injury 1
Syphilis 1
Hypertension (190 systolic) 1
Epidemic Meningitis 4
Pneumonia 1
Nephritis 1
Hydrocephalus and Mitral Regurgitation 1
Mitral Lesion and Streptococcus Septicemia 2
Undetermined 22

Most of these cases were children or young adults, and he suggests the possibility of accounting for many of them on the basis of an inherent weakness of the blood vessels. In support of his suggestion, he cites the fact that others have interpreted increased bleeding and coagulation times as evidences of certain hemorrhagic diatheses, and refers to Meylahn's conclusion that spontaneous meningeal hemorrhage nearly always occurs as a diapedesis.

Cobb and Hubbard[3] report five cases coming to autopsy with hemorrhages into the parenchyma of the brain as the result of venous stasis. Three were associated with sinus thrombosis and two resulted from asphyxia. In one, thrombosis occurred in the course of an otitis media and meningitis, another followed an inflammation of the pericardium, and the third was associated with extensive phlebitis in the legs and abdomen following an attack of broncho-pneumonia. All showed at autopsy congested blood vessels and diffuse areas of extravasation into the brain parenchyma, and in one there was extensive subarachnoid hemorrhage. In the cases of asphyxia, without blocking of the vessels, they concluded that hemorrhage resulted from cerebral anoxemia.

Symptoms

While most hemorrhages occur as the result of head injuries, the symptoms of those appearing as sequelae or complications in other conditions may be misinterpreted. Meningeal irrita-

*From the Pathological Laboratory of the Grady Memorial Hospital.

tion, choked disks, leucocytosis, and evenly distributed red blood cells in the spinal fluid constitute a diagnostic syndrome in most instances; but associated with moderate elevation of temperature, headache, vomiting, stiff neck, early motor changes, positive Kernig's and Brudzinski's signs, the symptoms may be mistaken for the early manifestations of meningitis.

Doyle[4] reports four cases of thrombosis of the superior longitudinal sinus discovered at autopsy but not diagnosed during life. He concludes that the "number, variety, and possible combination of symptoms depend on the type, size, and site of thrombus, the peculiarities of anastomosis of the cerebral veins, and ability of the cardiovascular apparatus to establish competent collateral circulation."

In one instance the ante mortem diagnosis was softening of the brain of infectious character; in another, abscess; in a third, cerebral hemorrhage; and in the fourth, tumor.

The first two followed operations for infections of sinus and mastoid. The third patient was a male, 28 years of age, with an adenoma of the thyroid gland, a basal metabolic rate of plus 27, and a blood pressure of 140/90. Twenty-four hours after admission, he had a severe headache and three days later convulsions of left foot, leg and thigh, and left upper extremities. On the fifth day he became cyanotic, stupid, and developed a left sided

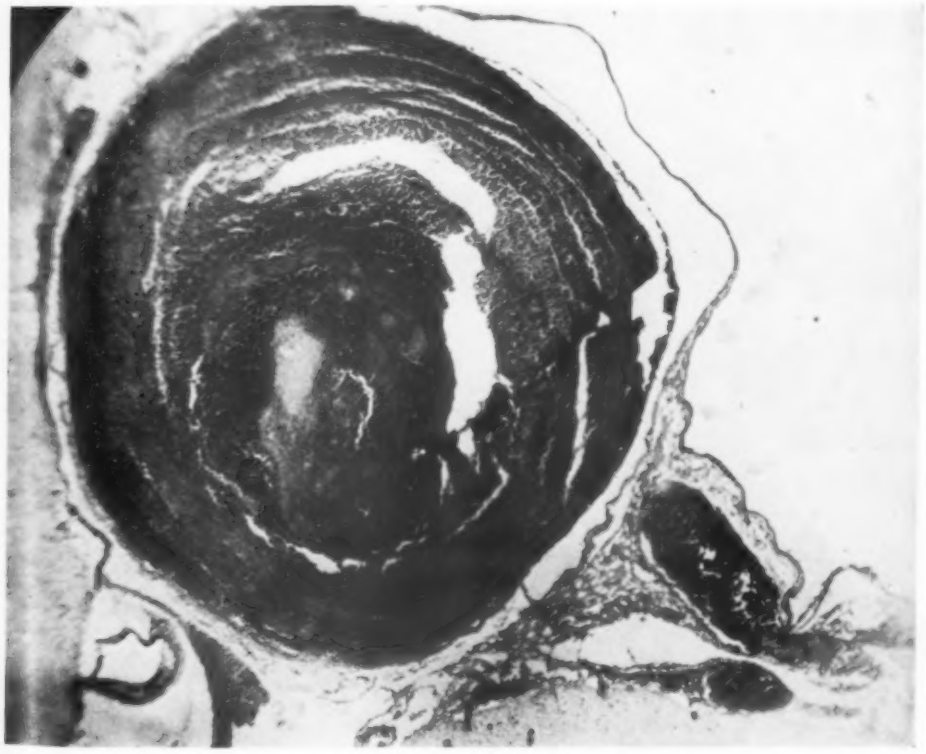


FIG. 1. Thrombosis of a superior cerebral vein.

hemiplegia and left homonymous hemianopsia. His spinal fluid was at first negative and later yellow tinged with pressures of 12 and 10 mm. On the seventh day he became comatose and died.

At autopsy there was thrombosis of the longitudinal sinus from the superior frontal gyrus to torcular Herophili with hemorrhagic softening of the right side of the brain from frontal gyrus to the calcarine fissure and of the left side in the region of the precentral and post-central gyrus.

The fourth case was a female, age 21, who six months before admission had recurring sudden right occipitocervical headaches associated with vertigo and vomiting. Three weeks before examination the syndrome recurred with stupor and incontinence. At the time of examination there was choking of both disks, swelling of face and eyelids, paresis of conjugate ocular movements upward and laterally, cervical rigidity, and slight incoordination of right extremities. For six months she had recurring attacks of headaches, vertigo, and vomiting. On reexamination, the left patellar and Achilles reflexes were exaggerated. Lumbar puncture was negative. She died; and at autopsy, thrombosis of the superior longitudinal sinus extending into both lateral sinuses was found.

Pathology

Regardless of etiology or manner of occurrence, subarachnoid hemorrhage

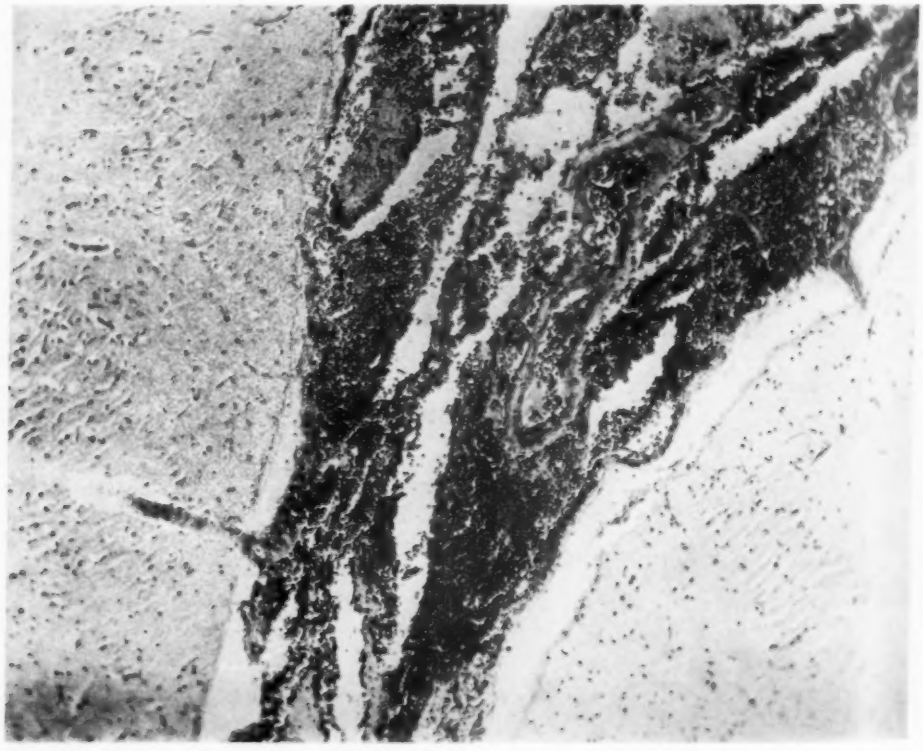


Fig. 2. Diffuse hemorrhage into subarachnoid space.

is commonly found at autopsy without gross lesions to designate the vessels concerned. Most of the blood is usually found about the base of the brain, and the third and fourth ventricle may contain clots.

The superior longitudinal sinus receives the superior cerebral vessels, veins from the diploë, dura, and pericranium; and at its origin, through the foramen cecum, it usually communicates with the veins of the nasal fossae.

Embolism and thrombosis may result, therefore, from widely separated focal lesions, and the resulting venous stasis within the pial vessels may easily account for diapedesis of erythrocytes, especially in the presence of hypertension.

Case Report

A housewife, 36 years of age and nine months pregnant, entered the hospital Feb. 18th, complaining of occipital headache, swollen feet and ankles. Her blood pressure was 200/138, and her urine contained from a trace to three plus albumen without red blood cells, casts, or pus. There were 22 mgs. of non-protein nitrogen, 2 mgs. of urea nitrogen, 90 mgs. of sugar, and 1 mg. of creatinin in 100 cc. of blood. The phenolsulphonphthalein output was 70% in two hours. Mosenthal test showed a range of specific gravity from 1.000 to 1.012, and a total urinary output of 1125 cc. in twenty-four hours. Her blood Wassermann was negative; and blood count 5,730,000 red blood cells and 11,800 leucocytes with 52% neu-

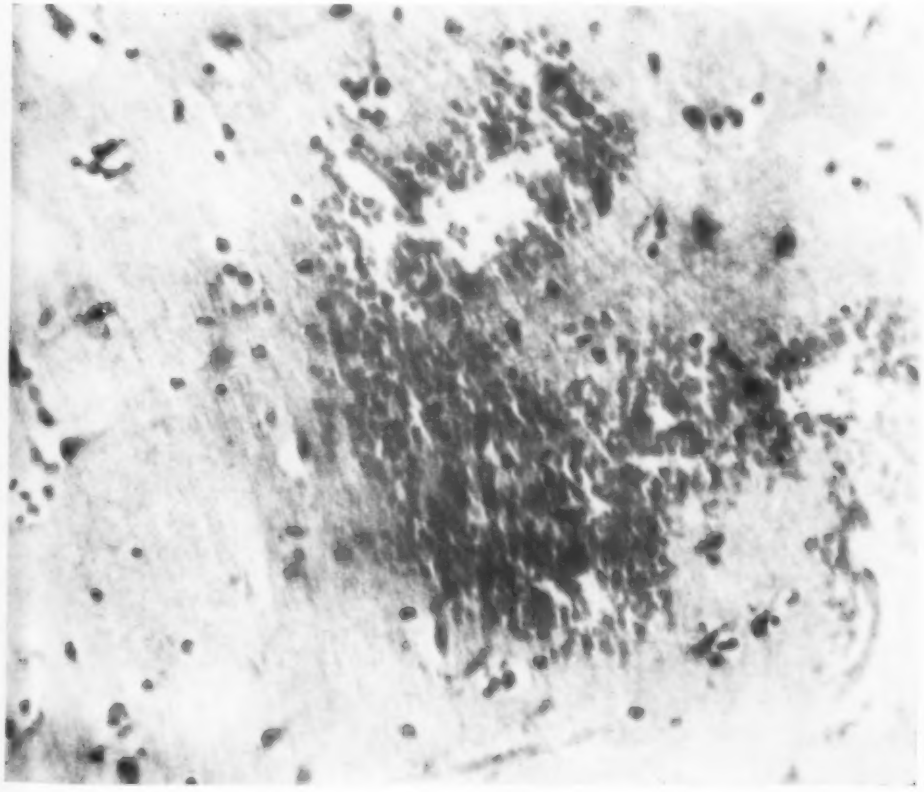


FIG. 3. Area of hemorrhage and degeneration in cortical parenchyma.

trophils. Aside from three pregnancies, complicated by ante partum eclamptic attacks, her past history was negative.

On admission her temperature was 98.3 F; pulse, 70; and respirations, 18. There was no cardiac enlargement, and the only abnormalities other than edema of the lower extremities were carious teeth and diseased gums. Ten days after admission she gave birth to a girl baby weighing four pounds and fifteen ounces. A week later she was sent home in relatively good condition. Her blood pressure at the time of dismissal was 140/110. Two days later, on March 9th, without apparent cause, she had a convulsion and the next day was returned to the hospital. She was received in a semicomatose condition, and from eleven forty-five to five fifty P. M. had ten generalized convulsive seizures lasting one half to two minutes each. Her blood pressure was 150/90; temperature 102° R; pulse, 120; and respirations, 30. During the next five days she gradually regained consciousness, but on the 12th her gaze became fixed and she had a short clonic convulsion of both lower extremities. Her blood pressure was 160/108. On the 14th her neck became stiff, Kernig's sign was positive, and there was bilateral papilledema. The spinal fluid was blood tinged and contained five leucocytes per cubic millimeter of fluid. Wassermann and colloidal gold tests were negative, and no bacteria were found on culture. 15 to 25 cc. of blood tinged spinal fluid were removed daily on the 14th, 15th, 16th, 17th, and 22nd.

On the 16th, she began to cough and complain of pain in the lower left side of the chest. There then followed limited expansion, distant breath sounds, and, on percussion, dullness from the angle of the left scapula downward. The leucocyte count increased to 18,600 with 91% neutrophils. On the 23rd, she became restless and talked at random. Her temperature reached 103° R; pulse, 144; and respirations, 44. She developed a right sided hemiplegia and died on the afternoon of the 24th, fifteen days after admission.

An autopsy was performed an hour after death. There was an abscess the size of a hen's egg at the posterior inferior border of the lower left lobe of the lung, and scattered areas of broncho-pneumonia and edema in both lower lobes. There was no growth of bacteria after 72 hours of incubation of the heart's blood in dextrose bouillon.

All cortical blood vessels of the brain were congested. The superior longitudinal sinus was filled with an organized thrombus which extended into the superior cerebral veins of both hemispheres. There were large areas of subarachnoid hemorrhage, especially over the left parietal and occipital lobes and over the right parietal lobe in the region of the longitudinal sinus. Cut surfaces showed no gross hemorrhage within the brain parenchyma. On microscopical examination, however, all blood vessels were engorged; and in the cortical substance of the brain, there were scattered large and small areas of edema and softening, with rare foci of extravasated red blood cells. About the thrombosed vessels of the pia there were larger extravasations into the subarachnoid space.

Other organs showed no gross or microscopical pathological processes.

Summary

The above pathological syndrome is recorded as an instance of subarachnoid hemorrhage resulting from sinus thrombosis and venous stasis.

Considering the subsequent pulmonary lesions, it might be suggested that thrombosis of the sinus originated as a phlebitis of the veins of the nasal fossae accompanying an upper respiratory infection. Arterial hypertension should have contributed to the diapedesis of red blood cells from the congested pial vessels.

[1] Smith, Wm. A.: Spontaneous Subarachnoid Hemorrhage, So. Med. Jour. 1930, 23: 494.

[2] Neal, J. B.: Spontaneous Meningeal Hemorrhage, Jour. Amer. Med. Assn. 1926, 86: 6.

[3] Cobb, Stanley, and Hubbard, Jno. J.: Cerebral Hemorrhage from Venous and Capillary Stasis. Am. J. Med. Sc. 1929, 178: 603.

[4] Doyle, Jno. B.: Obstruction of the Longitudinal Sinus. Arch. Neur. and Psych. 1927, 18: 374.

Gland Extracts in Experimental Carcinoma and Sarcoma of Albino Rats

By O. M. Gruhzit, M. D., *Research and Biological Laboratories, Parke, Davis and Company, Detroit, Michigan*

RECENT publications directed to the possible beneficial effect of organ extracts in cancer, have led us to evaluate a number of these extracts in experimental carcinoma and sarcoma of rats.

Experimental

A series of albino rats were inoculated with the Flexner-Jobling carcinoma* or Jensen sarcoma* of rats. When the tumor reached in size about one square centimeter, the animals were divided into three groups and placed under treatment. One group was treated with the hormone extract; the second group remained as untreated controls and the third group was placed on treatment with an extract of oxen testis prepared in a similar manner as the hormone extract. The group of tumor rats treated with the oxen testis extract served as a control for a non-specific protein effect.

The extracts were administered subcutaneously on the opposite side from the growing tumor. Six daily injections per week were given in maximum tolerated doses. On the death of the animals a careful necropsy was performed. Absence of plainly visible neoplastic tissues in the tumor was followed with a microscopic examination of fixed tissues for neoplastic cells.

The suprarenal cortex extracts were prepared either in accordance with a recent patented process**[1] or as described below. Since the above patented extract is of unspecified concentration, we adjusted it so that one cc. contained extractive material from one gram of fresh sheep cortex substance. In this concentration the extract contained traces of adrenalin. For convenience this extract is designated as cortex extract E.

For a comparative study, a suprarenal cortex extract from fresh beef suprarenal cortex material was prepared by mixing it with 1.6 volumes of 0.17 per cent hydrochloric acid and allowing it to stand for 45 minutes at room temperature. The mixture was then continuously stirred and gradually brought to 96° C. The mixture was then filtered through soft filter paper by gravity. The reaction was adjusted to pH 4.65. The clear filtrate was chilled overnight in the refrigerator

*Original tumor bearing rats were obtained from Dr. F. C. Wood and the U. S. National Institute of Health.

**U. S. Patent 1771976 granted to Coffey and Humber on July 29, 1930.

and filtered through a Mandler filter. One cc. of the extract represented extractive material of one gram of fresh gland cortex substance. The adrenalin content was equal to 1:2000. This extract for convenience was called cortex extract A.

A portion of the above extract was saturated with sodium chloride and filtered. The filtrate was discarded. The residue was dissolved in acidulated water so that one cc. corresponded to one gram of fresh cortical material. The reaction was adjusted to pH 4.65. The solution was chilled and filtered through a Mandler. The adrenalin content was equal to 1:40,000. This extract is referred to as cortex extract B and is practically free from adrenalin.

The thymus extract was prepared according to published directions[2] and contained per cc. extractive substances equivalent to 0.6 grams of fresh glandular tissue.

The oxen testis extract C was prepared in accordance with the process used for cortex extract E, but was adjusted so that one cc. represented extractive substance from 0.5 gm. of fresh testis gland. The testis extract D was prepared in a similar manner as the cortical extract A and it was adjusted so that one cc. contained extractive substances from 0.5 gm. of fresh testis gland.

The cortical extract A was administered at first in 0.12 cc. and was increased to 0.25 cc. per day for eighteen injections in twenty-one days. This treatment was followed with the extract B in 0.25 cc. doses and increased to 0.5 cc. per day for seventeen injections in twenty-one days. The oxen testis extract was given at first in 0.2 cc. doses and later it was increased to 0.4 cc. per day for thirty-six injections in forty-two days. The control carcinoma rats remained untreated.

In Figure 1 it is noted that the Flexner-Jobling carcinoma growth in rats of series I under treatment with cortical extracts A and B of high and low adrenalin content respectively, at no time showed regression in the size of the tumor during a period of forty-two days with thirty-six injections.

The Flexner-Jobling carcinoma in albino rats treated with the oxen testis extract D of 0.2 to 0.4 cc. per day with a total of thirty-six injections in forty-two days at the end of forty-nine days had caused no regression of the tumor growth. The growth of the tumor materially did not differ from that of the control or from the animals treated with cortical extract of high or low adrenalin content.

The tumor growth in the control animals in this series behaved similarly to the treated rats. The greater size of tumors in this control group after the first twenty days is accounted for by the death of a few animals with smaller tumors, thus considerably increasing the average tumor size of the remaining animals. In none of these Flexner-Jobling carcinoma tumor bearing rats did the tumor growth regress and disappear.

Another group of rats of series 2 similarly inoculated with Flexner-Jobling carcinoma, but containing twenty to twenty-nine tumor bearing animals in each of the three groups, besides a group of rats of series 3 with tumors ulcerated and far advanced, were placed on suprarenal cortex extract E. This extract was administered

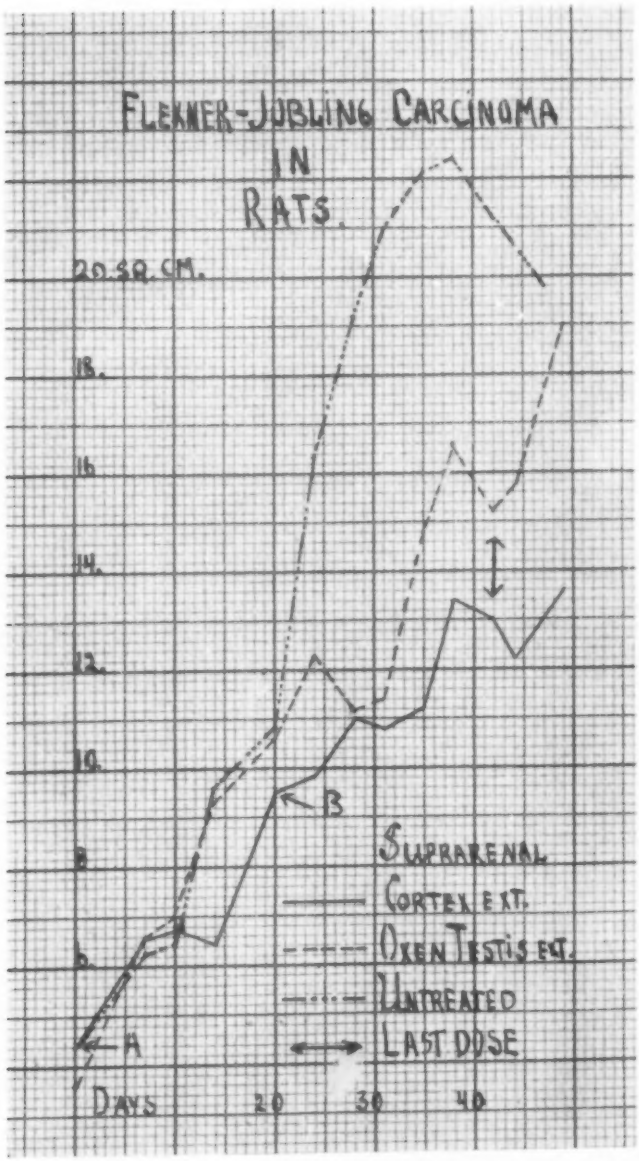


FIG. 1. The Rate of Growth of Flexner-Jobling Carcinoma in Albino Rats Under Treatment with Suprarenal Cortex and Oxen Testis Extracts as Compared with Untreated Tumor Bearing Rats.

beginning with 0.0625 cc. per day and increasing rapidly to 0.15 cc. in six days for twelve injections and then the dose was increased to 0.2 cc. daily and carried until the end of the experiment of nine weeks.

A similar group of twenty-eight tumor bearing rats was placed on treatment with oxen testis extract C prepared in a similar manner to the cortex extract E. This extract was given to rats in 0.2 cc. daily. The third group of twenty carcinoma bearing rats remained untreated.

The carcinoma growing tumors in rats treated with 0.5 cc. thymus extract (2) per day, behaved in all essential respects similarly to the ones treated with the suprarenal cortex, oxen testis or to untreated controls, as noted in Figure 2, although with a less rapid rate of growth. The examination of the tumor masses of the thymus treated animals at no time indicated a dis-

TABLE I. The Average Rate of Growth of Carcinoma Tumor Per Rat Under Treatment with Suprarenal and Oxen Testis Extracts as Compared with Non-Treated Controls.

	Rats	Before Treatment	Weeks After Treatment								
			1st Sq. Cm.	2nd Sq. Cm.	3rd Sq. Cm.	4th Sq. Cm.	5th Sq. Cm.	6th Sq. Cm.	7th Sq. Cm.	8th Sq. Cm.	9th Sq. Cm.
Series 2											
Cortex Ext. E	29	3.5	6.1	7.6	10.3	14.3	15.1	17.3	19.2	18.9	20.7
Oxen Testis C	28	3.1	4.1	5.4	8.1	11.9	13.8	13.3	18.0	14.0	13.0
Untreated	20	2.8	4.0	5.3	7.9	10.5	14.1	15.2	16.2	18.6	17.2
Series 3											
Cortex Ext. E	7	6.51	8.44	9.74	13.6	12.92	16.92	18.95	–	–	–
Untreated	6	6.49	9.51	15.70	18.42	22.30	26.35	26.51	–	–	–

It is evident from Table I that during the nine weeks of treatment with the suprarenal cortex extract E and testis extract C, neither of the glandular extracts had a retarding effect on the Flexner-Jobling carcinoma tumor growth, and if anything, the rate of growth of the tumor in rats treated with the suprarenal cortex extract E was more rapid in comparison with the oxen testis extract treated carcinoma tumor bearing rats. The treatment with the cortical extract E in rats in which the tumor was ulcerated and far advanced was similarly ineffective as shown under series 3. The treated and the untreated rats of this series died at appearance of the neoplastic tissues. The treatment neither delayed the tumor growth nor did it cause its regression. All tumor bearing animals, treated or untreated, died.

Simultaneously with the study of the effect of the different gland extracts on Flexner-Jobling carcinoma in rats, these extracts were used in the treatment of Jensen sarcoma tumors in albino rats. The effect of the extracts in sarcoma bearing rats is illustrated in Figures 3 and 4. The suprarenal cortex extract A with a high adrenalin content, 1:2000, extract B with a low adrenalin content, 1:40,000, and pure adrenalin in dilution of 1:1000, were

given daily in doses of .125 cc. to 0.5 cc. respectively for 16 to 25 days.

From Figure 3 it is evident that neither of the suprarenal cortex extracts possessed more action than adrenalin alone, nor that the effect of these extracts differed from that of testis extract or untreated controls. The greater effect of adrenalin, 1:1000, on the sarcoma tumors was only casual and could not be duplicated in other experiments.

The non-effectiveness of the various organic extracts in sarcoma of rats is

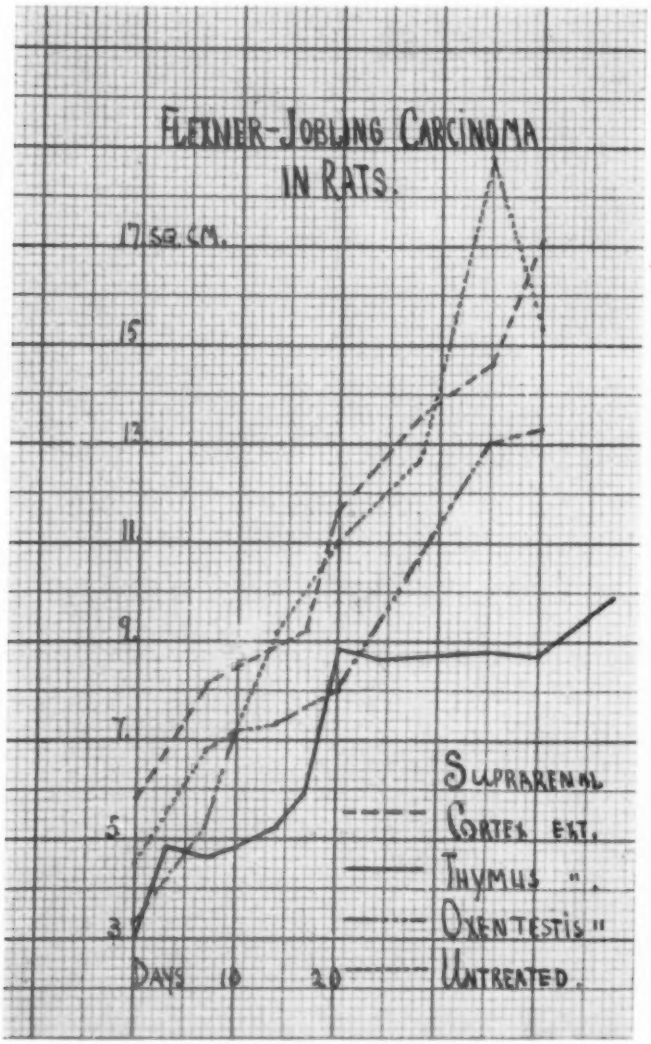


FIG. 2. The Average Rate of Growth of Flexner-Jobling Carcinoma of Rats Under Treatment with Suprarenal Cortex, Thymus and Oxen Testis Extracts in Comparison with Untreated Tumor Bearing Rats.

even more clearly brought out in the case of the thymus extract, and omentum extract, as contrasted with untreated controls (Figure 4).

The thymus extract was used in 27 rats daily for 29 days in doses of 0.25 to 0.5 cc. The rate of tumor growth and its decline is almost similar to that of the control group. The tumor reached the maximum growth irrespective of the treatment and the animals usually died from complications or absorption of the toxic necrotic material of the tumor. The death of the rats with larger tumors, leaving the smaller tumor bearing rats alive, is responsible for the abrupt decline in the curve. The untreated control tumor bearing rats show similar changes in the tumors as noted in Figure 3.

The omentum extract was made by extracting hog omentum with 80 per cent ethyl alcohol. One-half of a cc. of the water-soluble part was given daily to tumor bearing rats for a period of 22 days. The rate of tumor growth under the treatment with this lipoid extract from omentum was entirely comparable with the gland extracts. The tumors neither receded nor did the neoplastic tissue disappear.

The relation of ulceration of the neoplastic tumors in rats under the treatment with the various gland extracts is alluded to by Bishoff[2] as a possible effectiveness of the treatment with an organic extract. In Table II the incidence of ulceration is presented for Flexner-Jobling carcinoma in albino rats.

It is noted that the incidence of ulceration is less in untreated than in treated animals. The incidence of ulceration under mineral salt administration (lactate salts of magnesium and calcium and potassium acid phosphate, one cc. intravenously twice weekly of equal parts of 3, 10 and 10 per cent respectively) is considerably greater than in tumor bearing rats treated eith-

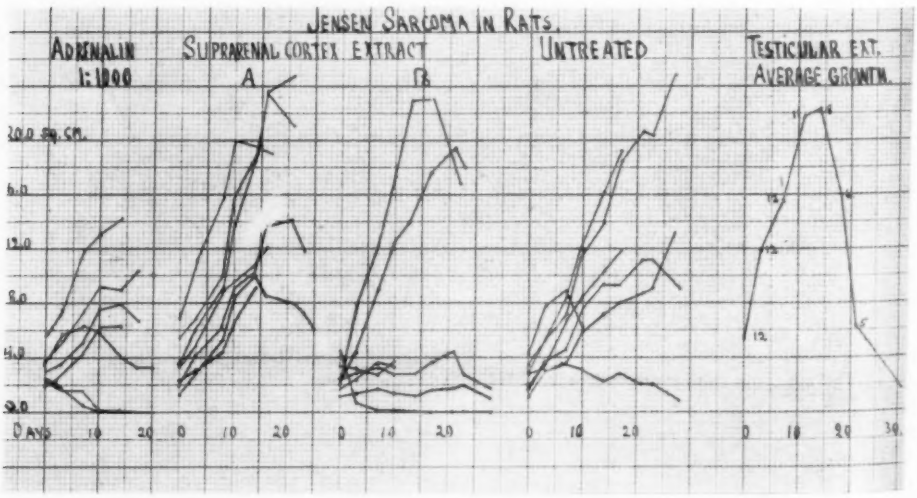


FIG. 3. The Rate of Jensen Sarcoma Tumor Growth Under Treatment with Suprarenal Cortex, Adrenalin and Oxen Testis Extracts as Compared with Untreated Controls.

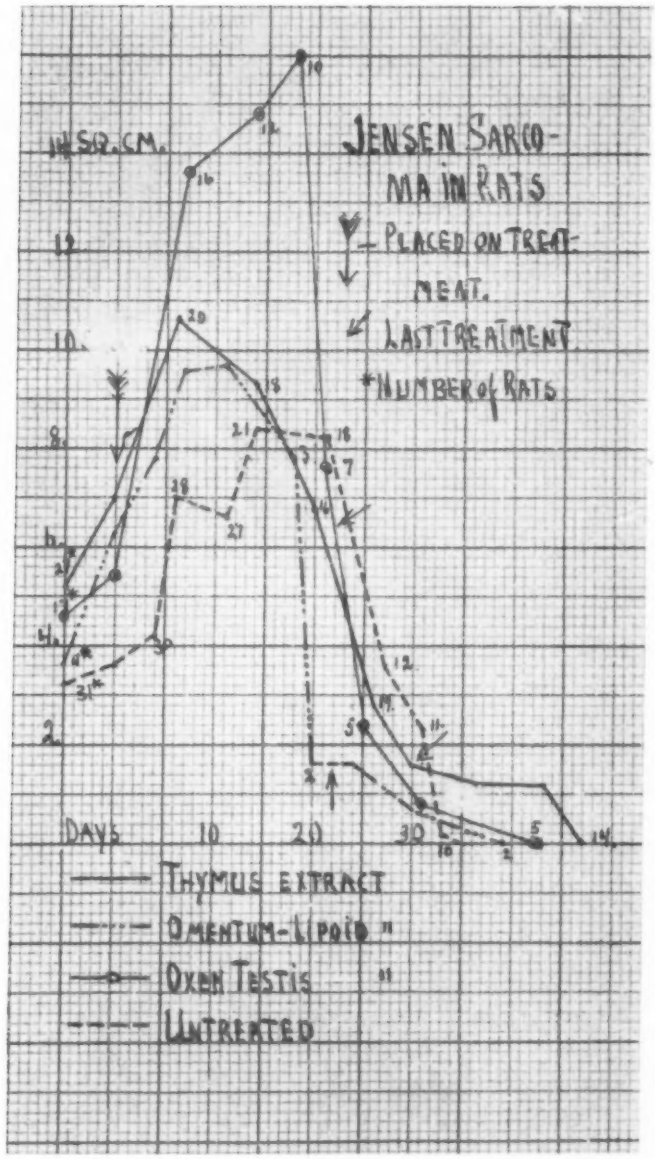


FIG. 4. The Average Rate of Jensen Sarcoma Tumor Growth Under Treatment with Thymus Extract, Omentum Lipoid Extract and Oxen Testis Extract as Compared with Untreated Tumor Bearing Albino Rats.

TABLE II. The Incidence in Per Cent of Ulceration in Carcinomatous Tumors in Rats Treated with Cortical, Oxen Testis Extracts, A Mixture of Magnesium, Potassium and Phosphate Salts and Untreated Controls.

	Original No. Rats	Weeks After Treatment							
		1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Series 2										
Cortex Ext. E	29	10	22	33	51	65	74	87	95	95
Oxen Testis Ext. C	28	8	28	28	41	67	70	70	75	77
Untreated	20	–	12.5	12.5	25	67	71	82	82	82
Series 3										
Mineral Salts	7	29	57	57*	71	86	100	—		
Untreated	6	—	—	—	—	50	65	82		

*First week following cessation of mineral salt treatment and continued on suprarenal cortex extract E.

er with oxen testis or suprarenal cortex extracts. The oxen testis extract treated rats show about the same per cent of ulceration in a given period as those treated with the cortex extract. It is apparent that none of the gland extracts caused more ulceration in carcinoma tumors in rats than could be similarly noted in animals treated with oxen testis extract or non-protein mixtures of some of the common salts of magnesium, calcium, etc.

Discussion

The Flexner-Jobling carcinoma and Jensen sarcoma growth in albino rats represents a foreign body which derives its nutrition from the circulating blood stream of the host. Any substance circulating in the blood stream *in apriori* reaches these tumor cells and exerts an action. The spontaneous tumors in animals or man are in an intimate relation with the normal structures of the host and may or may not be influenced by the substances in the blood stream. In our series of Jensen sarcoma the average spontaneous regression was about twenty-five per cent. In the case of Flexner-Jobling carcinoma the tumors regressed spontaneously on an average of about ten per cent. The expectancy of regressions of the foreign body type of tumors under treatment should be considerable if the treatment possessed any action. Neither Bishop and Maxwell's findings with sarcoma in rats, nor our results with carcinoma and sarcoma, suggest the slightest effect of the suprarenal cortex, thymus, omentum-lipoid or oxen testis extracts upon tumors in the tumor bearing animals.

Itami and McDonald[4] in a recent paper, could not demonstrate a beneficial effect of true suprarenal cortex hormone of Swingle and Pfiffner in spontaneous breast carcinoma in mice.

Summary

1. Albino rats inoculated with Flexner-Jobling carcinoma, when treated with different suprarenal cortex substance extracts both with high and low adrenalin content, showed neither a delay in the growth of the tumors or their regression as compared with either untreated tumor bearing rats or those treated with a non-specific protein extract of oxen testis.

2. The treatment with thymus extract neither inhibited the growth or

caused the carcinoma tumors in rats to regress. Injection of the extract did not prolong the life of the tumor bearing animals.

3. The suprarenal cortex extracts with high or low adrenalin content, the thymus, the omentum-lipoid and the oxen testis extracts neither inhibited growth nor caused regression of the Jensen sarcoma tumors in albino rats.

4. The rate of ulceration of carcinoma tumors under treatment with various gland extracts was not greater, as compared with the rate of ulceration of similar tumors in rats under treatment with inorganic salts or with a non-specific extract of oxen testis.

5. The organic extracts studied in experimental carcinoma and sarcoma in rats had no beneficial effect in inhibiting growth of the tumors, their regression, nor did the extracts cause prolongation of life of the tumor bearing animals, as compared with untreated tumor bearing animals or those treated with non-specific protein extracts.

BIBLIOGRAPHY

[1]Coffey, W. B. and Humber, L. D.: Extract of Adrenal Cortex Substance. California and Western Medicine 33: 640, 1930.

[2]Hanson, A. M.: Treatment of Cancer with Thymus Extract. J.A.M.A. 94:652, 1930.

[3]Bishoff, F. and Maxwell, L. C.: Hormones in Cancer. Jour. Pharm. and Exp. Therapy 40: 97, 1930.

[4]Itami, S. and McDonald, E.: Adrenal Cortex Extracts and Cancer. Science 72 (no. 1870): 460, 1930.

Amebic Dysentery: Sugar Cane as a Possible Distribution Hazard*

By Mills Sturtevant, M.D., F.A.C.P., *New York*

OCCASIONAL cases of amebic dysentery have been seen in large clinics in the United States for forty years[1,2]. Amebic dysentery has, however, been regarded until about fifteen years ago as a tropical disease.

Since 1916 epidemics, sporadic cases, carrier cases, infected individuals who have never been out of their respective localities have all been reported from France[3,4], England[5,6,7], Canada[8] and the United States[9,10,11]. Three editorials have appeared in the Journal of the American Medical Association[12,13,14], calling attention to reports of the disease in twenty-four states and suggesting that cases may be expected in any locality in the United States. Feder[15], Musser[16], Dowling[17], Brown[18], Kaplan, Williamson and Geiger[19], Craig[20] and others have written of cases seen in a variety of localities.

Conveyance of the cysts to man so that he swallows them and becomes infected may be by food or water. It has been suggested that rats[21], cats and flies[22] may have a part in distribution of the cysts. Infected market gardeners, food handlers and cooks have been mentioned as distribution hazards.

Two cases have come to the attention of the writer where another possibility is suggested.

Patient A. A. was admitted to Bellevue Hospital September 25th, 1927, 20 years old, a dishwasher. He was a native of Salvador, Central America and had been in this country two years, all of the time in New York. Thirty-three days before admission the patient began to have loose movements which increased in frequency and became bloody. Three or four movements at first soon became ten to fifteen a day. With this he had cramplike pain in the abdomen which also increased rapidly in severity. This was relieved by bowel movement. Proctoscopic examination revealed ulcers which Dr. Elmer I. Huppert thought were characteristic of emebic dysentery. Dr. Joseph Connery found and identified the *Endamoeba histolytica*.

No good lead could be discovered as to the source of this infection with the following exception. The patient had a friend whom he had known in Salvador and who worked on a boat plying between New York and Salvador. Three days before the onset of his symptoms and thirty-six days before

*From the Department of Medicine, The University and Bellevue Hospital Medical College, New York University and The Third Medical Division, Bellevue Hospital.

admission he had visited his friend on a boat which had just come in from Central America. The friend had brought some sugar cane and our patient had enjoyed several stalks, biting into the stalk and sucking the juice. This seemed a possible manner of infection.

Patient A. C. applied for treatment October 24th, 1928. He was 30 years old and had always been well until a year before when he had contracted diarrhoea in Los Angeles. This had persisted with an average of 5 or 6 movements a day and 1 to 3 at night. The movements were bloody and accompanied by lower abdominal pain. Bowel movement relieved the pain to a great extent. Proctoscopic examination showed ulceration which suggested amebic infection. Dr. Joseph Connery found and identified *Endamoeba histolytica.*

This patient at the time of the onset of his disease had been working on the dock in Los Angeles. He had helped unload boats from various ports and had eaten some sugar cane. He did not know that any of his fellow workmen who also ate the sugar cane contracted diarrhea.

Conclusion

Two individuals with proved amebic dysentery are cited who had eaten of sugar cane brought from the tropics. Since no other likely method of infection of these persons could be discovered it is suggested that sugar cane may carry the cysts of the *Endamoeba histolytica.*

REFERENCES

[1]Osler, W.: On the Amoeba Coli in Dysentery and in Dysenteric Liver Abscess. Bull. Johns Hopkins Hosp. 1:53 (May) 1890.

[2]Lafleur, A.: Demonstration of Amoeba Coli in Dysentery. Bull. Johns Hopkins Hosp. 1:91 (Sept.) 1890.

[3]Ravaut, P. and Krolunitsky: Amoebic Dysentery. Presse méd. 24:22, April 17, 1916.

[4]Bloch, M. and Matlei, C.: Amoebiasis on French Front. Annales de Médicine. 5: 4, September, 1918. 374.

[5]Worster-Prought and Rosewarne, D. D.: Amoebic Dysentery in Man Who Had Never Left England. British Medical Journal, I, 2890, May 20, 1916.

[6]Baylis, H. A.: Incidence of Endamoeba Histolytica. Lancet, I, 2, Jan. 11, 1919.

[7]Simpson, A. S.: Amoebic Dysentery Contracted in England. Lancet, II, Sept. 4, 1926, 495.

[8]Bates:, Abstr. in Jour. A. M .A .86: 377, 1926.

[9]Kofoid, C. A., Kornhauser, S. I., and Plate, J. T.: Intestinal Parasites in Overseas and Home Service Troops of the U. S. Army. Jour. A. M. A. 72: 1721, 1919.

[10]Cort, W. W. and McDonald, J. D.: Amoebic Dysentery in California, Journal of Infectious Diseases, 25: 501, 1919.

[11]Stiles, C. W.: Public Health Status of Amoebic Dysentery in the United States as Potentially Influenced by World War. Boston Medical and Surgical Journal, 186: 377, 1922.

[12]Jour. A. M. A. 76:21, May 21, 1921, 1405.

[13]Jour. A. M. A. 80:9, March 3, 1923.

[14]Jour. A. M. A. 84:9, Feb. 28, 1925, 678.

[15]Feder, J. M.: Intestinal Amoebiasis, Journal of Laboratory and Clinical Medicine, 12; Feb., 1927, 456.

[16]Musser, J. H.: Amebiasis. American Journal of Med. Sci. 174: July, 1927, 1.

[17]Dowling, G. A.: Amoebic Infection in the State of Washington. Jour. A. M. A. 81:20, Nov. 17, 1923, 1657.

[18]Brown, P. W.: The Nature, Incidence and Treatment of Endamebiasis. Jour. A. M. A. 86:7, Feb. 13, 1926, 457.

[19]Kaplan, B., Williamson, C. S., and Geiger, J. C.: Amoebic Dysentery in Chicago. Jour. A. M. A. 88:13, March 26, 1927, 977.

[20]Craig, C. F.: The Symptomatology of Infection with Endameba Histolytica in Carriers. Jour. A. M. A. 88:1, Jan. 1, 1927, 19.

[21]Kessell, J. F.: Host-Parasite Relationships of Certain Intestinal Protozoa Important to Medical Zoology. Jour. A. M. A. 90:14, April 7, 1928, 1089.

[22]Acton, H. W. and Knowles, R.: Dysenteries in India, Calcutta, 1928.

Reasons for the Artist's Conception of the Physician

By Ben Wolepor, M.D., *Philadelphia, Pa.*

JOSEPH CONRAD defined the artist as one who in a moment of courage, snatched from the remorseless rush of time, a passing phase of life; one who attempted the highest kind of justice to the visible universe by bringing to light the truth. The artist appeals to that part of our being which is not dependent on wisdom; to that in us which is a gift and not an acquisition—and therefore more permanently enduring. This is an eloquent and stirring description but far from a true one. The artist cannot describe truth in its entirety. His vision is often distorted by an inner myopia. He is subject to the vicissitudes of life which temper his art. One needs but regard the works of Goldsmith and Crabbe. The former wrote a cheerful poem of a village in which youth disported on the green and enjoyed life to the full; the latter described a harrowing scene, in which ingratitude and feeble old age predominated. The villages described resembled many other English communities of the period but the different personalities of two great poets regarded the same object in a markedly different way.

An artist is the instrument of his age, a victim, as are all men, of its weakness and a participant in its glories. He differs in that he gives voice to the views of his contemporaries. At times he becomes prophetic and foresees the future if he possess the piercing vision of genius that annihilates the differentiation of Time, that makes the present and the future merge into one. This is indeed a rare quality. He is a favored mortal if he be only one who makes his age articulate rather than one who is the instrument of the world and of all time; then only does the artist fulfill Conrad's conception of him. Then does the poet, looking deeply within himself, see certain fundamentals which are universal and to which his gift of words gives permanence.

The artist has a difficult task. He must describe emotion, the most fluid and evanescent of all energies. He must first feel deeply so as to give his work the stamp of sincerity and then make others participate in scenes spun from the imagination. No matter how skillful he may be, he often fails to convey his complete conception of life. Anatole France has repeatedly stressed the inadequacy of words which at the best are only deficient symbols of

*From the Graduate School of Medicine, University of Pennsylvania.

thought. The artist's perpetual question is "How does this phase of life affect me?" and not, "What is the truth?" The truth is a matter of secondary importance to most artists. His chief task lies in interesting his reader and then, if he be fortunate, of informing him. He resorts to artifices of all types and grossly exaggerates so as to captivate the imagination. It would be futile to expect Flaubert or Swift to deal justly with the world, condemning its vices but upholding its virtues. Equanimity is the goal of the philosopher but not that of the poet.

The Artist As Judge

Despite the idiosyncrasies of the artist, his command of words gives him power which he often utilizes to attack groups of men of whom he disapproves. He is frequently correct in his appraisal of a situation but is only too often more zealous than righteous and lends verisimilitude to gross error. When he attacks Medicine he unfortunately at times finds a rich field to garner. Medicine is an honorable profession but is subject to fluctuations that occur in races, science and the Arts. In Medicine periods of decline follow those of ascent; during an interval of low ebb the vigilant eye of the critic may spy a conspicuous defect which forms the nucleus of a pitiless drama. He bases his argument upon enough truth to erect an elaborate but untrustworthy superstructure.

The tragedy of Medicine lies in its continuous dying and being reborn. In the words of Ecclesiastes "The wind goeth toward the south, and turneth about unto the north; it whirleth about continually, and the wind returneth again according to his circuits." Medicine makes progress and like the wind, goeth toward the south and then disaster overtakes the world, new disrupting tendencies appear that engulf all man's progress; knowledge comes to a standstill; Medicine languishes with all the other arts, and, again like the wind, turneth about unto the north and whirleth in the doldrums of universal inactivity. With a renewal of truth and light and a dispersal of ignorance, Medicine, in conjunction with the other products of man's intellect, returneth again according to his circuits.

The Medical profession had deteriorated in France in the 17th century. It was divided into three armed and battling camps, those of physicians, surgeons and barbers. They disliked and despised one another. Raynaud says that "Our fathers, absorbed as they were by learning and philosophy, by endless debates, only too often forgot that medicine is learned at the bedside. It may appear incredible, but the majority of students secured their Bachelor of Medicine degree without ever having seen a single patient. In brief, the practical side of Medicine which in our opinion supersedes everything, was then most neglected. Their desire was to shine in oratorical display. One might with truth have assumed that Medicine was only a branch of literature."

The age provided Molière with a great opportunity for the rapierlike thrusts of his wit. He thought that because doctors could not cure him and had killed his only son that they were pretentious ignoramuses; men who quoted Hippocrates and when corrected said, "Nous avons changé tout cela."

"They had," he thought, "changed everything for the worst, these rogues who wore wigs and red heels, made ostentatious use of their learning and instead of taking care of their patients, talked at great length of technical things." Molière dragged Sganarelle from the gutter, a drunkard who beat his wife and starved his children, who sold all the furniture in the house to buy liquor, and laughingly made a physician of him. In a knowing way he says, "Behold a doctor who pleases me; I think he will succeed, because he is a clown."

Molière was a great dramatist but he was not impartial nor did he adhere closely to the truth. He had an axe to grind. He was embittered by the loss of his son, by his poor health. He was also a writer of comedies who sought continuously for good material; therefore he cheerfully sacrificed the truth of the situation in order to depict the medical profession as consisting of men who when called into consultation, discuss the relative value of a mule as compared with a horse. The age that Molière ridiculed was that of the great anatomists Bartholin, Riolan, Pecquet, Littré, Winslow. Doctors, at the time, according to Raynaud, formed a teaching body; a lucrative and honoured profession, accessible only to the higher ranks of the middle class. The welfare of one doctor had to be sacrificed to the interests of all to maintain the profession intact. The Faculty of Medicine of Paris was not opposed to progress but desired that advancement in knowledge come from her and not from foreign lands. She frowned upon the view of the circulation of the blood not because it was an untenable theory but because an Englishman was the discoverer.

Molière did not regard the universe as a sequence of events. He described an isolated instance, the condition of Internal Medicine in France in the 17th century and condemned all doctors. This was far from an historical perspective. He was unaware that Sydenham was proclaiming to a rather weary world the views of Hippocrates, or that Harvey was writing his "De Motu Cordis"; but then, rebellion was in the air. Molière, like so many other great men was a product of the age and his very individualism was part and parcel of an egotistical, yearning, rebellious period. Cervantes thrust Don Quixote against the antiquated windmills of tradition. Bach took music and made a towering edifice of it. Rembrandt merged the indignant faces of his subjects into the general scheme; Milton waged a mighty conflict in which God triumphed over a glorious though fallen angel; one who would not accept defeat but in the midst of flame and chaos hurled denunciations at his victor. Strife was in the air. Traditions toppled over like dead trees in a storm. Freedom of thought, like a gust of wind freed man's mind from intellectual cobwebs. Bruno was to die at the stake. Acosta was to kill himself in defiance of a world that repudiated good motives supported by intellect because they were at variance with prevailing thought. Great men may have much to do with the moulding of a period but they themselves are greatly influenced by their age. One doubts

whether Shakespeare could have written his plays and sonnets in any age but the Elizabethian.

THE ARTIST REGARDS THE DOCTOR

Disillusioned Flaubert gave scant consideration to Charles Bovary, the hardworking country practioner and to Homais, the apothecary. He made a dupe of the former, one who lacked the vision to satisfy the romantic yearnings of an erotic wife; of the latter he made a garrulous fool. To understand an artist's conception of life one must know the artist, his relationship with life, his success or failure. Some men, like Shakespeare or Spinoza, resemble the falcon. They breast the storm; fly above the dark clouds, scream at the lightning. They will not admit defeat; but nevertheless their lives and works show the effects of the storm. They have conquered, but at a cost, and gained Heaven by way of Calvary. Flaubert was not made of Shakesperian fibre. He could write "Madame Bovary," but not "The Tempest." The odds were against him. Even as a boy he could not face failure and consequently confronted with difficulties, as one with his personality would be, became a youthful cynic. "This is a fine civilization," he cries, "an age that has invented railways and prisons, rectal pumps, cream tarts, royalty and the guillotine." He was tortured by an unceasing imagination, the curse that afflicted Madame Bovary.

The young, oversensitive Flaubert suffered at school intensely. He, like Shelley, met defeat at the hands of his schoolmates. He could not contend with a collective egotism which developed in him a deep aversion to humanity. His ideas and unsociability were ridiculed. Tormented by his teachers, laughed at by his comrades, he sought refuge in solitude. He writes that Byron and Rabelais are the only two who have written with the intention of hurting and laughing openly at mankind. "I am incessantly dissecting; it amuses me and when I have at last laid bare corruption in something, which is thought to be fine, found gangrene in beautiful things, I lift my head and laugh. I've come to hold the firm conviction that vanity is at the base of everything." Flaubert, the analyst of human vanities, revealed at seventeen his future aesthetic formula. "I had nothing to cling to" he says, "neither society nor solitude, nor poetry nor science, nor skepticism nor religion. I was only a mummy embalmed in my own sorrow." Then he acquired epilepsy, an incurable disease. How could Flaubert write truthfully of life? He who knew life only through his own dismal sensations. Charles Bovary was a failure, Homais a fool, Madame Bovary, a disillusioned heartbroken counterpart of Flaubert who, unable to stand the boredom of life, committed suicide. The story is compounded of a sequence of tragedies. It may have been truth, but only a facet of the gem called life; no more truthful in its entirety than Eugene O'Neil's "The Strange Interlude." These men and women are inhabitants of a madhouse. They crave the impossible and like spoiled children, cry because they cannot play with the moon. There is no hope for them. They are doomed from the start, for within them lies no nucleus of future battles. Defeat has stamped them in the cradle and they

bear the grisly mark to the grave. Flaubert bears witness to the bias of the artist, the impinging of his personality on his work.

Bernard Shaw is a vigorous antagonist of the medical profession and makes the illuminating statement that the main distinction between a quack doctor and a qualified one is the fact that only the qualified one is authorized to sign death certificates for which both sorts seem to have equal occasion. He sweeps away with a blithe hand all the drudgery which the average medical student undergoes to acquire his M.D. He gallantly darts into the turbulent sea of immunity of which he knows nothing and discusses vigorously subjects from which even an experienced metaphysician, shrinks. Shaw's conceit makes him ignore the preliminary education essential even for remote glimpses into immunity, a subject which occupies the entire attention of masters; for the theory of 1920 is only too often the fallacy of 1930. Obsessed with what he conceives to be the utter worthlessness and cruelty of animal experimentation, the rock upon which physiology is based, he ascribes man's desire to learn to a specific lust for cruelty which infects even his passion of pity and makes it savage. Led by a preconception, he wages a bitter conflict with medicine; totally unaware of his bias, he utilizes his wit to lash at what he conceives to be the bane of the age, the medical profession. He makes amusing but fallacious reading.

"I do not know," he writes, "of a single thoughtful and well-informed person who does not feel that the tragedy of illness at present is that it delivers you helplessly into the hands of a profession which advocates and practices the most revolting cruelties in the pursuit of knowledge. As to the honour of doctors, they have as much as any other class of men, no more and no less. And what other group of men pretend to be impartial when they have a strong pecuniary interest on one side. There is another difficulty in trusting to the honour and conscience of doctors. Doctors are just like other Englishmen; most of them have no honour and no conscience. All that can be said for medical popularity is that until there is a practicable alternative to blind trust in the doctor, the truth about the doctor is so terrible that we dare not face it."

Divergence of Views That Artists Hold on the Same Subject

Bernard Shaw is justly considered as a notable man of letters. Anatole France is one of the greatest writers his country has produced. Mark Twain has a large following and yet the divergence of their views on as important a person as Jeanne D'Arc is impressive.

The Maid revolutionized Europe. A staunch Catholic, she instituted the belief, to the astonishment of the Church that she loved, that man was responsible to God alone for his actions. She wept when refused the privileges of the Church, yet stoutly affirmed that her mission was from God.

Shaw, who usually refuses to take anything seriously, strangely regards Jeanne as sane and offers an ingenious but inadequate argument to prove his point. He insists that Jeanne's voices and visions were illusory because they

deserted her at a crucial moment, at a time when she needed their reassurance and comfort most, during her trial. When she was led to the stake and La Hire failed to batter down the gates of Rouen, when Warwick, who desired her speedy death, remained in power, she recanted. She donned woman's garb, which to her meant abject humiliation and the shattering of the bright vision that had led her on to victory, that had enabled her to crown the Dauphin king, at Rheims Cathedral. Shaw therefore assumes that this highly logical step was the product of a sane, orderly mind. He ignores the fact that insanity is a refuge for the mentally afflicted, that Jeanne created a visionary world because the every day one did not give her the gratification she derived from an imaginary sphere.

Her early youth was marked by stigmata upon which psychiatrists lay great stress. Seclusive, a dreamer, who watched her father's sheep, she peopled the green meadows of Domremy with angels who spoke to her. Saint Marguerite, Saint Catherine and Michael came down from the Heavens to talk with a child of twelve. They gave her advice and she would embrace them, intoxicated by their presence and fragrance. They were very intimate and oftentimes when it was dusk and she could not see them, they spoke to her from the bells. The quiet of the evening, the peace of the fields brought to her the voices of St. Michael and Saint Catherine that she loved, that guided her to glory and the stake. Her heart that was impelled by heavenly guidance was cast into the river Seine. She was not of this earth; she was a Saint, a genius, abnormal. Her recantation, due to imminent peril was transient. She reverted to her miraculous world because it was the only one in which her tortured mind could find peace. What though it led to the stake and a pitifully prolonged death? The flames that embraced her body and the waters of the Seine that received her heart were only physical agents. The power and intensity of her mind have survived to the amazement of a rather mechanical age.

Anatole France, scholar, artist, approached the truth more closely than did Shaw. Great enough to realize that keen observation and a skilled pen are not sufficient in themselves to thoroughly understand a person who requires medical attention, he sought the aid of Dr. G. Dumas, a French psychiatrist, who reservedly made the diagnosis of Hysteria in Jeanne D'Arc. Anatole France approached Jeanne in an uncharitable spirit. He would not understand the Maid or her age. To properly appreciate his views of her one need only study his "Thais." He made of this courtesan a splendid creature indeed. Beautiful, admired, surrounded by luxury, sought by the gifted and distinguished, she led a riotous existence. Then seeing the first faint imprint of age, remembering a scene of her childhood in which a Christian slave took part, she sought refuge in that institution which welcomes the sinner. She ended as gloriously as she had lived. She tasted life to the full and died sanctified.

The spirit of Anatole France permeates the book. It is his Credo. He reverts to it time after time. It contains the commandment of "Thou

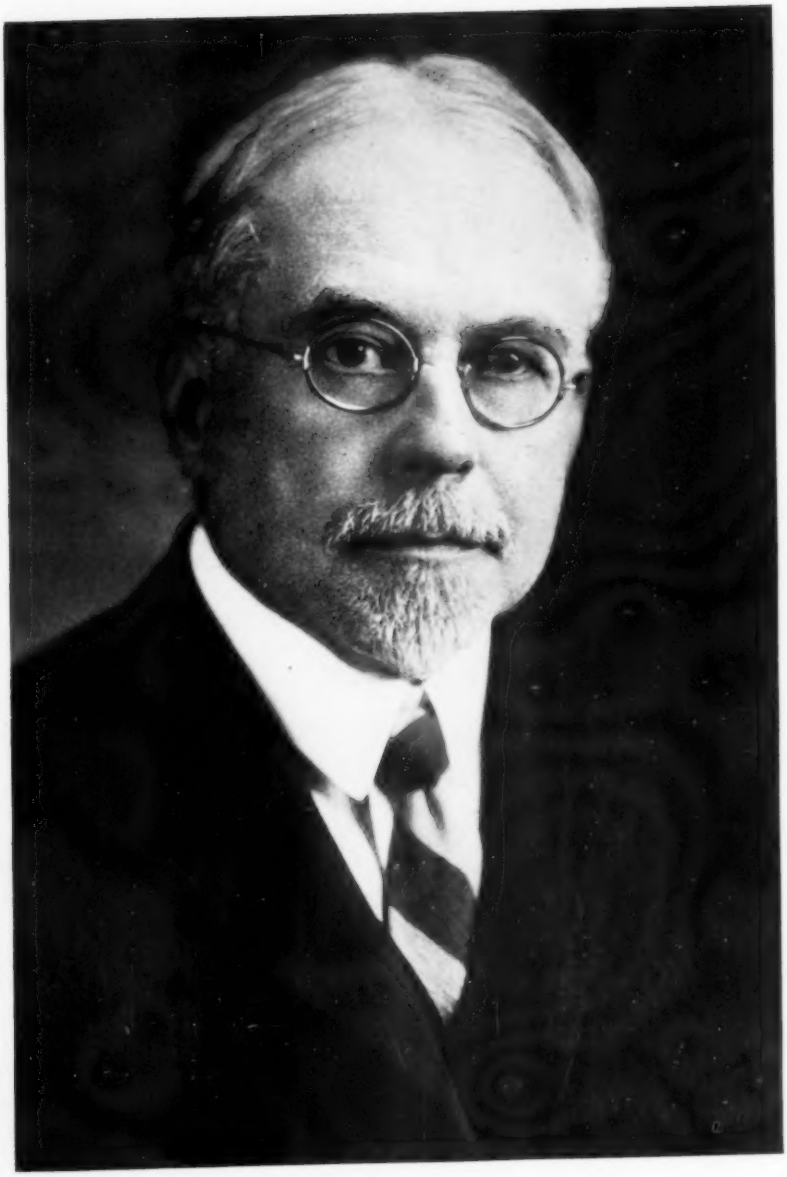
shalt not let joy pass thee by. Life is gratification." Paphnuce, the lover of Thais, who leaves her to enter the desert; who lies on a hard rock and does penance, has a sorry end. France despised him, and condemns him to an ignoble death. He was incapable of understanding renunciation. Abstention was to him not only a negative but a hideous quality. It was not life, it was the denial of life. He thought that Paphnuce was a fool and Thais justified.

He could understand Mary Magdalene but not Jeanne D'Arc. She wore man's clothes, this incomprehensible creature, fought like a man; slept on the floor side by side with her comrades-in-arms; charged the English at the head of her soldiers, was wounded by an arrow which pierced her breast and died at the stake uttering the name of Jesus, seven times. France was an ardent desciple of Voltaire and carried in his heart his Master's words, "Ecrasez l'infâme." France disliked the Church although he was capable of deep religious conviction as his "Christ de L'Océan" testifies; the religion of motives rather than that of formulae was his belief.

The world has been fortunate in possessing an accurate narration of the Maid's trial. Despite this reliable evidence, two prominent authors, Shaw and France, disagree utterly on crucial points, her sanity, her methods. Shaw believed her sane, a good soldier and a statesman. France asserted that she was insane, that Dunois was the brains behind it all and that clerical prompting was responsible for her religious zeal. He denied that she had marked military and political ability.

Mark Twain made a very ladylike creature of a domineering warlike maid, an incongruous picture. He avoided the real Jeanne D'Arc. He preferred that which Shaw terms a Victorian lady.

The artist whether he judge Maid or physician often differs from his fellow craftsman on crucial points. He sees through the veil of his early training, bias and mental make-up. His views resemble those of many historians; they make delightful fiction. The truth is often not in them. Shaw will move mountains to gain a point. France repudiated motives which he admired intensely because they lay in the heart of a religious girl; one so devout, that she died for the Church she loved, crying out the name of her God who died as she had. The Maid will live despite her burning and the physician will still heal the ill, comfort the dying, despite all the Molières, Flauberts, and Shaws of the world.



Aldred Scott Warthin, 1866-1931

Editorial

Aldred Scott Warthin

Through the death of Aldred Scott Warthin the American College of Physicians has lost not only a Master, its First Vice-President, and the Editor of the ANNALS since 1924, but also a wise counselor and loyal friend. Once convinced of the intrinsic value of the College, he gave freely to it of his time and energy. With that foresight which characterized also his scientific investigations, he was able to visualize the important place which the College was to occupy and the extent to which it was to become a potent factor in fostering high standards of achievement in Internal Medicine and its related branches. This prophetic vision and this faith are most happily finding justification and realization, but Dr. Warthin was far from being satisfied for he felt that, after all, the College was only entering upon its career of usefulness. In a letter to President S. Marx White, dictated less than forty-eight hours before his death and left unsigned, Dr. Warthin said, in part: "I think that I would like to be on the program next year at the California meeting. So many men have written to me concerning various matters pertaining to the College that I would like to make an address bearing upon the future of the College and its functions. * * * * The editorial which I had in the number preceding the meeting of the College apparently excited a good deal of thought, and I am glad to see that there is a growing appreciation that the College should some time have something more than mere scientific work. * * * * I think that there is a real opportunity to make the College a more vital force and influence in American Medicine than it is at the present time." Doctor Warthin must have had concrete suggestions in mind as he dictated these words. What they were, we can only surmise in part, but we can be sure that they were constructive and not destructive, for he would have planned the fullest possible utilization of existing agencies. The counsels which he had in mind, one can be sure, had had opportunity for crystallization during that period when time for reflective deliberation was provided by an enforced absence from the laboratory and its daily hurried routine, but they were not conceived in that interval. They were the outgrowth of a rich experience, forty years as a teacher, investigator and clinical pathologist. How rich this experience was, is revealed in the historical sketch which appears elsewhere in this number of the ANNALS. His major research activities alone show a breadth of interests which goes far to explain why Dr. Warthin has exerted a significant influence, although usually an unconscious one, in the affairs of the Col-

lege. The first four years of his teaching experience, under Doctor George Dock, were devoted to Internal Medicine. It was during this period that the then young Demonstrator of Internal Medicine described in one of his early papers the accentuation of the pulmonary second sound in pericarditis and assigned diagnostic significance to it. This alteration in the quality of the heart sounds has since been known as 'Warthin's sign.' The same ability to make detailed objective scientific observations and to deduce from them conclusions, oftentimes at variance with prevailing views or far in advance of them, characterized his entire career as an investigator. Moreover, while Dr. Warthin believed fully in the value of pure science and in the worth of research for its own sake, he was always able to perceive the clinical application of new facts and to turn them to practical account. In his description of the hemolymph nodes and demonstration of them as organs *sui generis* together with other studies upon the blood-forming system, he anticipated our present conception of the reticuloendothelial apparatus — only that cumbersome, yet convenient, name was lacking. His early recognition of the importance of the thymico-lymphatic constitution, followed more recently by other studies upon pathological constitutional types as they are related to the etiology of neoplasms, pernicious anemia and Graves' disease, showed his appreciation of the importance of an aspect of the causation of disease which has not yet received the general acceptance which it deserves. As early as 1904, and again in 1906, he vigorously recorded his belief in the genetic unity of the group which includes the lymphosarcomas, chloroma, the leukemias and Hodgkin's disease, and he lived to see most workers in this field accept this generalization. The first of the long series of papers on the pathology of syphilis appeared in 1910. Concerned originally with the lesions of congenital syphilis, Dr. Warthin soon recognized the essential unity of the pathology of syphilis as found in various organs and in various stages of the disease. Fortifying his position by the demonstration of the causal organism in lesions in which its presence had never before been proven—largely through original methods developed in his own laboratory—he founded a new conception of the pathology of latent syphilis and described the characteristic lesions as they occur in the heart, aorta, pancreas, adrenals and testes. But in this, as in all his other work, it was the clinical application which was uppermost in his mind. These few illustrations will serve to show the manner and degree in which all of Dr. Warthin's investigative work aided in making him an important factor in American Medicine and in the College. But to knowledge, to experience and to clinical judgment, there were added personality and character. Unusually apt in public address, energetic and convincing in his manner of presentation, Dr. Warthin's share in the programs of the College never failed to provoke thought. Fearless, honest and above suspicion of ulterior motives, he was able to criticize without arousing animosity. He imparted some of his own energy to every phase of the activities of the College with which he

was concerned. An attempt, then, on the part of anyone else to formulate those suggestions which Dr. Warthin proposed to offer at the California meeting must be feeble, if not presumptuous. We can be sure that they would have been wise, practical, constructive, unselfish and inspiring. It is not unlikely that he would have urged consideration of ways and means for securing more general social and intellectual contact between the members of the College—something more than the contact of the "shop." A greater emphasis, too, upon the cultural aspects of Medicine, and upon the value of those recreational activities, such as medical book-collecting, which are natural by-products of the thoughtful pursuit of Medicine, would have been proposed. Certainly, too, he would have discussed the importance of casting the weight of influence of the College against the wholesale adoption of temporarily popular, but actually ephemeral, methods of diagnosis and treatment, for he felt strongly that too often, in the espousal of "fads," physician and patient are alike deluded; and that here, if anywhere, there is a weak link in the chain of medical economics. Long and close association leads us to believe that we are right in these assumptions. How fortunate would the College have been, and how grateful and happy we all, if Aldred Scott Warthin had lived to give the College his message! Yet his influence will do much to guide its course for years to come.

Abstracts

The Use of Cortin in Addison's Disease. By FRANK A. HARTMAN, A. H. AARON, and J. E. CULP. (Endocrinology, 14:438-442 (Nov.-Dec.), 1930.)

As previously shown by Hartman and his associates, cortin, a substance obtained from the adrenal cortex, enables adrenalectomized cats and rats to survive indefinitely. If Addison's disease is due to a deficiency of cortin the injection of this substance should ameliorate the disease. A patient, a man 24 years old, who was apparently moribund, has been kept alive for more than five months by this method. When first seen he was in shock with a pulse pressure of 50/20 mm. He was cold and drowsy, complained that his extremities felt numb, and talked irrationally. Twenty-four hours after admission, 5 cc. of cortical extract was injected intravenously followed by further sub-cutaneous injections in 10 cc. quantities until 150 cc. had been given in 24 hours. Under this régime there was marked clinical improvement, particularly after the third day. The amount of cortin administered was gradually reduced until he was receiving only 20 cc. in 24 hours. On the eleventh day there was a severe relapse, followed by symptomatic improvement when the dosage was again increased. Five months after treatment was instituted the patient was still much improved clinically. Four relapses had occurred, each following reduction of the dosage. A few hours after increasing the extract after each relapse, improvement was evident, and in two or three days recovery was almost complete. The appetite returned and mental activity became normal. It is difficult to account for these effects except through the action of cortin. Each relapse was accompanied by a fall in blood pressure and a rise in blood urea. Blood sugar was low during or after a relapse.

Experimental Production of Acute and Chronic Nephritis by the Injection of Bismuth Compounds. By PASTEUR VALLERY-RADOT, MAURICE DÉROT, and Mlle. P. GAUTHIER-VILLARS. (Revue Belge des Sciences Médicales, 3:319-323, April, 1931.)

By the intramuscular injection of an oily suspension of bismuth hydroxide the authors were able to produce in young rabbits evidences of acute, sub-acute, and chronic nephritis with azotemia, albuminuria, and tubular lesions in the kidneys. The suspension used contained the bismuth compound in an amount equivalent to 0.0646 grams of metallic bismuth per cubic centimeter. The doses employed in the production of nephritis were from 8 to 17 times greater than those used therapeutically in man. With the introduction of 0.50 cc. daily, per kilo of rabbit, all the animals used showed an azotemia which was independent of malnutrition. Some showed a transient albuminuria. Death occurred in from 9 to 17 days. With daily injection of 0.20 cc. of the suspension, the animals survived from 37 to 75 days. Chronic intoxication was accomplished by using smaller amounts or increasing the interval between successive doses. Histological changes were found to be in accord with those noted by others. Glomerular lesions were relatively slight, consisting of congestion in the earlier cases, intracapsular serous exudate and in four instances evidence of proliferation of the endocapsular lining. Tubular changes were to be found especially in the convoluted segments and varied from swelling of the tubular epithelium to complete necrosis and desquamation. Calcification in the renal tubules occurred in ten animals. In one, dying on the ninth day, it was so marked as to render the cutting of sections difficult. (*Note by Editor.* These and simi-

lar investigations of the effects of bismuth compounds upon the kidneys are of great importance. There can be no doubt that the relatively insoluble salts of bismuth, when administered over long periods of time, as is often the case in self-medication, may produce a chronic tubular nephritis. When this occurs the histological changes are essentially the same as described above.)

On the Principles of Renal Function. By GÖSTA EKEHORN. (Acta Medica Scandinavica, Supplementum xxxvi, 1931.)

This monograph of 717 pages presents the results of an investigation extending over a period of four years, the experimental portion of which was performed at the University of Oxford in the laboratory of Dr. J. G. Priestley. By glomerulo-puncture, but with refinements in micro-physical and micro-chemical methods, which are minutely described, the glomerular urine of frogs was made available for volumetric titration and comparison with the blood and with the bladder urine of the same animal. The author concludes that at present it is impossible to formulate more than a fragmentary explanation of how the urine is normally formed, and still less is it possible to explain the pathological aberrations from the normal. As to the long-standing questions of filtration and resorption *or* renal secretion, however, he definitely favors the former to the exclusion of any form of selective secretion. The glomeruli filter and the resulting filtrate is produced in a volume which is from 100 to 200 fold that of the resulting bladder urine, the rate varying a good deal under different conditions. The tubules elaborate the filtrate into urine exclusively by reabsorbing into the blood the excess water and the excess amounts of all other urinary constituents contained in the large volume of filtrate; they resorb quantitatively from the filtrate all diffusible plasma constituents that fail to appear in the bladder urine. It is possible, although there is no definite evidence, that some of the metabolic products of the tubular epithelial cells may be added directly to the urine during this process. It is unlikely that the composite fluid reabsorbed by the tubules is of constant composition as held by Cushny, and it is especially because of this that it is necessary to await further data in order to be able to construct a complete theory of normal and pathological renal behavior.

The Relation of Monilia Psilosis to Tropical Sprue and an Evaluation of Fermentation of Sugar as a Criterion for Specificity. By BAILEY K. ASHFORD. (The Porto Rico Journal of Public Health and Tropical Medicine, 6:310-333, March, 1931.)

Of 163 cases of clinical sprue, 127, or 77.9 per cent were positive for *Monilia psilosis;* 14, or 8.5 per cent, were positive for an atypical *Monilia psilosis;* another 14 were positive for a monilia similar to two strains which were converted by passage into *Monilia psilosis.* On the other hand, of 76 cases which were not sprue, *Monilia psilosis* was found in 14, or 18.4 per cent, but 13 of these were manifestly suffering from indigestion or diarrhea. Of 178 presumably healthy persons, only 5.6 per cent were found to be carriers. Sprue is generally insidious, and it complicates many slowly progressive fatal diseases of the tropics such as tuberculosis, cancer and dysentery. Malnutrition is usually the real basis for sprue, and upon it sprue is usually engrafted. In 50 per cent of such cases, not clinically sprue, a typical *Monilia psilosis,* or some nearly related or atypical form thereof, has been found in the feces. Some of these may be clinically unrecognizable cases of sprue. This does not prove that *Monilia psilosis* is the cause of sprue. Favorable conditions provided by a diseased digestive system may offer a medium for a harmless saprophyte. However, if this organism is a proven pathogen elsewhere, as in the tongue of thrush, the lung, tonsils, bone and skin, one should be guarded in stating that it is not related to sprue. The fermentation reactions, cultural characteristics and morphology of the organisms investigated in connection with the study of this large series of cases led to the suggestion that *Monilia albicans, Monilia psilosis, Monilia Pinoyi,* and others may be one and the same yeast-budding fungus first described by Robin in 1853.

Reviews

Laboratory Medicine: A Guide for Students and Practitioners. By DANIEL NICHOLSON, M.D., Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba; Assistant in Pathology, Winnipeg General Hospital. 433 pages, 108 text figures and colored plate. Lea and Febiger, Philadelphia, 1930. Price, $6.00, net.

In this book will be found detailed information on the indications, methods and interpretation of useful laboratory tests that a medical practitioner should be able to do. More highly technical diagnostic procedures which are apt to be performed in a large laboratory are also discussed as to the principles involved and proper interpretation. Preceding the technical section there are a number of charts and outlines indicating the choice of tests in various disease conditions. Some teachers of Internal Medicine will object to this card-index approach to the subject. The laboratory procedures proper are presented in fourteen chapters beginning with the methods of examination of the blood and ending with a description of essential laboratory equipment and lists of reagents. This book will prove to be of great value to the practitioner who performs the simpler tests himself, particularly those that can be done at the bedside; and will be useful to the laboratory technician. Technical methods for the preparation of microscopical sections of tissues are omitted except for the rapid method described by Terry. Since this guide is not intended for institutional laboratories, this omission is doubtless wise, for an adequate presentation would have added too much to the size of the book. Unfortunately, the ability to diagnose tissue sections is not as casual a matter as is indicated by the statement that study of illustrations in the best texts in pathology and surgery and review of permanent sections will qualify the surgeon to interpret microscopic pictures.

Textbook of Human Embryology. By CLEVELAND SYLVESTER SIMKINS, Ph.D., Associate Professor of Anatomy, University of Tennessee Medical School, Memphis, Tennessee. With 263 illustrations, some in colors. xiv+469 pages. F. A. Davis Company, Philadelphia, 1931. Price, $4.50, net.

This textbook of embryology should prove to be of more than usual interest to medical students because it lives up to its title in that whenever possible the descriptions of developmental processes are specifically those which apply to man. Only when direct evidence is not available from human material are other mammals utilized and then specific information is given as to wherein probable differences occur. Likewise, there is a frequent correlation of morphology with the functional aspects of development which tends to bridge the gap between pure embryology and anatomy on the one side, and normal and pathological physiology on the other. The sections on aberrations and arrests of development, while very brief, have a similar value in respect to teratology. The illustrations are very well chosen from many sources and are excellently reproduced in keeping with the good press work of the entire book. The bibliography would have been made more useful by grouping the items in sections or by page references to the text. This book can be highly recommended to the student, and also to the medical practitioner who subjects himself to the, by no means arduous, discipline of occasionally reading a new text in each of the pre-clinical branches.

Human Physiology. By F. R. WINTON, M.D., Lecturer in the Department of Physiology and Biochemistry, University College, London; and L. E. BAYLISS, Ph.D., Assistant in the Department of Physiology and Biochemistry, University College, London; with a chapter on The

Physiology of the Sense Organs by R. J. Lythgoe, M.D., and a foreword by G. Lovatt Evans, D.Sc. (Lond.), F.R.C.P., F.R.S. xiv+583 pages. 227 illustrations. P. Blakiston's Son and Co., Inc., Philadelphia, 1931. Price in cloth, $4.50.

This book has been kept somewhat shorter than the usual major textbook of general physiology by restricting its subject matter more closely to that applying to the human animal, by omitting much anatomy, histology and biochemistry usually found in such books, and by leaving out practically all historical data. It aims to include all the factual material expected of the student in medical examinations. Well written and well printed, it is a book which is sure to give satisfaction to the student group. Carefully selected references point the way for those who wish to go more deeply into special fields. The introduction of numerous short excursions into the field of pathological physiology, such as caisson disease (but why was the word capitalized?) and hyperthyroidism will enliven the book for the average medical student; and is in accord with the general tendency in medical education to introduce clinical material at an earlier period in the curriculum.

The Vegetative Nervous System: An Investigation of the Most Recent Advances. The Proceedings of the Association for Research in Nervous and Mental Disease, December 27th and 28th, 1928. Editorial Board: Walter Timme, M.D.; Thomas K. Davis, M.D.; Henry Alsop Riley, M.D. xi+832 pages; 185 illustrations, and 19 tables. The Williams and Wilkins Company, Baltimore, 1930. Price, $10.00.

This is Volume IX in the series of research publications of the Association for Research in Nervous and Mental Disease. Under sections dealing with the Morphology, Physiology, Experimental Investigation, Clinical Investigation and Therapy of the vegetative nervous system, are grouped the contributions of forty-five investigators, selected because of special interest and training in their respective fields. Adequate review of the subject matter of so many papers cannot be attempted, but the entire group constitutes a very complete, almost encyclopedic, presentation of the most recent knowledge in this field. Because of the breadth of treatment, this monograph will be extremely useful to those working in the preclinical subjects, such as anatomy and histology, physiology and pathology, as well as to the clinical investigator and practitioner.

Treatment of Epilepsy. By Fritz B. Talbot, M.D., Clinical Professor of Pediatrics, Harvard University Medical School; Chief of Children's Medical Department, Massachusetts General Hospital. xiv+308 pages. The Macmillan Company, New York, 1930. Price, $4.00.

It is intended that this book, concerned primarily with treatment, will supplement the monograph on epilepsy by Lennox and Cobb. It is much more than a therapeutic guide, however, for the author establishes the foundation for his major thesis by brief, well-written chapters dealing with the history, incidence, etiology, pathology and symptomatology of the disease. While other forms of therapy and management are discussed in appropriate sections, the second half of the book is devoted almost exclusively to dietary treatment, and, in particular, to the ketogenic diet. A bibliography of 306 selected references and an unusually detailed index complete the book, which can be recommended without reservations to those physicians interested in the care and treatment of epileptics.

Household Physics. By Walter G. Whitman, Head of Department of Physical Science, State Normal School, Salem, Massachusetts; Editor of General Science Quarterly. viii + 437 pages. 329 illustrations. John Wiley and Sons, Inc., New York City, 1930. Price, $2.50, net.

This addition to the Wiley Technical Series gives simple well-illustrated explanations of the physics of many forms of household apparatus and of their operation. Such relatively modern contrivances as the small home refrigerating plant are discussed. This should be a useful book in the nurses' training school library, and will answer not a few questions for the doctor himself. Thus fortified, he may even succeed in securing some respect for his erudition and scientific acumen from those of his own household.

College News Notes

NOMINATING COMMITTEE FOR 1932

In accordance with the provisions of the By-Laws, Article I, Section 3: The President "shall appoint within one month after induction to office a Nominating Committee of five, composed of two members of the Board of Regents, two members of the Board of Governors and one Fellow at large, whose duty it shall be to nominate candidates for the elective offices, Board of Regents and Board of Governors. The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective states, provinces or districts which will be represented by the nominees, if elected. The list of nominees for President-Elect and for the first, second and third Vice Presidents shall be submitted to all the Masters and Fellows of the College at least one month before the annual meeting, and the election of all nominees shall be by the members of the College at its annual business meeting. This does not preclude nominations made from the floor at the annual meeting itself," President S. Marx White, of Minneapolis, appointed the following Committee:

W. Blair Stewart, Governor
Edward L. Tuohy, Governor
Noble Wiley Jones, Regent
John H. Musser, Regent
Alfred Stengel, Fellow at Large, Chairman.

Dr. Mills Sturtevant (Fellow), Clinical Professor of Medicine at New York University, delivered a course in "Gastro-Intestinal Symptoms as an Approach to Diagnosis" in connection with an eight weeks' postgraduate course in Gastro-enterology recently given at the Health Center Building, Paterson, N. J., by the New Jersey Medical Society in co-operation with Rutgers University Extension Division.

Dr. George B. Eusterman (Fellow), Rochester, Minn., spoke before a joint meeting of the North End Medical Society and the North Branch of the Philadelphia County Medical Society at Philadelphia, May 7; his title being "Achlorhydria, Its Significance in Clinical Medicine and Gastro-Enterology."

In the May, 1931, issue of THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, Dr. John B. Youmans (Fellow), Nashville, Tenn., is the author of an article entitled, "Changes in the Skin in Thyrotoxicosis. With a brief study of the Absorption Time of Intradermally Injected Salt Solution in Patients with Thyrotoxicosis."

The sixtieth annual session of the California Medical Association was held at San Francisco, April 27-30, under the Presidency of Dr. Lyell C. Kinney (Fellow), San Diego.

Dr. Alexander T. Cooper (Fellow), Denver, addressed the Medical Society of the City and County of Denver, April 7, on "Some Observations on the Results of Phrenico-Exeresis in Pulmonary Tuberculosis."

The following Fellows of the College participated on the program of the Illinois State Medical Society's recent and annual meeting as indicated:

Dr. Walter M. Simpson (Fellow), Dayton:

"Recent Developments in Tularemia"

Dr. LeRoy Sante (Fellow), St. Louis:

"Factors Concerned in Radiation Therapy of Malignant Disease"

Dr. William W. Duke (Fellow), Kansas City:

"Allergy as Related to the General Practice of Medicine"

Dr. Edwin C. Ernst (Fellow), St. Louis: "Present Status of Penetrating X-Rays and Radium in Deep-Seated Cancer and other Diseases"

Dr. Walter C. Alvarez (Fellow), Rochester, Minn., spoke before the Iowa State Medical Society, May 13-15, on "The Art of Medicine."

Dr. Alvarez also gave the twentieth and last of the series of lectures at the New York Academy of Medicine, April 17, on "Problems of Gastro-Enterology Today."

Doctors Clifford A. Barborka (Fellow), and William C. MacCarty (Fellow), both of Rochester, Minn., were guest speakers at the sixty-fifth annual session of the State Medical Association of Texas, May 5-7. Their subjects were "Present Status of the Ketogenic Diet and Its Use" and "Classification, Diagnosis and Prognosis of Neoplasms," respectively.

Dr. James Marr Bisaillon (Fellow), Portland, Ore., addressed the Arizona State Medical Association on "End-Results Following Intrapleural Pneumolysis."

The Los Angeles County Medical Association was addressed, April 16, by Dr. John V. Barrow (Fellow), Los Angeles, on "Significance of Teeth in Focal Infections."

Dr. James H. Hutton (Associate), Chicago, addressed the Kane County (Ill.) Medical Society, April 15, on "Relationship of Endocrinology to Obstetrics and Gynecology."

Dr. Robert C. Moehlig (Fellow), Detroit, spoke before the St. Clair County (Mich.) Medical Society, recently on endocrinology.

Dr. Hugo A. Freund (Fellow), Detroit, was one of the speakers at the meeting of the Saginaw County (Mich.) Medical Society on March 17. He delivered an address on arthritis.

Dr. Samuel H. Snider (Fellow), Kansas City, Mo., addressed the Nodaway County (Missouri) Medical Society, recently, on "Artificial Pneumothorax: the Other Lung."

Dr. Joseph C. Doane (Fellow), Philadelphia, spoke on "What the Public Thinks of the Present Day Practice of Medicine" at a meeting of the fifth councilor district of the Medical Society of New Jersey, Atlantic City, April 10.

The annual meeting of the New Mexico Medical Society was held at Albuquerque, May 20-22, under the Presidency of Dr. Meldrum K. Wylder (Fellow), Albuquerque.

Dr. William Gerry Morgan (Fellow), Washington, D. C., addressed the one hundred and twenty-fifth annual meeting of the Medical Society of the State of New York, which was held in Syracuse, June 1-3.

The following Fellows of the College conducted a course in Internal Medicine at St. John's Hospital, Tulsa, which was attended by 135 physicians of northern Oklahoma:

Dr. John H. Musser (Fellow), New Orleans, La.

Dr. Charles A. Elliott (Fellow), Chicago, Ill.

Dr. Porter P. Vinson (Fellow), Rochester, Minn.

"Applied Therapeutics" was the subject of an address delivered by Dr. Arthur C. Morgan (Fellow), Philadelphia, April 9, before the Cambria County (Pennsylvania) Medical Society and the Cambria-Somerset Counties Pharmaceutical Association.

Dr. John O. Manier (Fellow), Nashville, and Dr. Ernest R. Zemp (Fellow), Knoxville, were re-elected Treasurer and Speaker of the House of Delegates, respectively, at the annual meeting of the Tennessee Medical Association.

Dr. Zemp presented a paper on calcium therapy before the Green County (Tennessee) Medical Society, recently.

Dr. George R. Minot (Fellow), Boston, delivered the annual Alpha Omega Alpha

lecture at the Vanderbilt Unversity School of Medicine, recently, on treatment of anemia.

Dr. William R. Bathurst (Fellow), Little Rock, Ark., was recently re-elected Secretary of the Arkansas Medical Society.

The New Haven County (Connecticut) Medical Association was addressed by Dr. John H. Foster (Fellow), Waterbury, on upper respiratory tract infections.

Dr. Allen H. Bunce (Fellow), Atlanta, recently addressed the Ninth District (Ga.) Medical Society on "Focal Infection—Is It a Practical Theory?"

Dr. Herman N. Bundesen (Fellow), Chicago, coroner of Cook County since 1928, was appointed Health Commissioner of Chicago by the newly elected Mayor.

Dr. Samuel A. Overstreet (Fellow), Louisville, Ky., addressed the Floyd County (Indiana) Medical Society, April 10, on "X-Rays in Gastric and Intestinal Disorders."

Dr. Oval N. Bryan (Fellow), Nashville, spoke before the Christian County (Kentucky) Medical Society, April 21, on undulant fever.

Dr. Virgil E. Simpson (Fellow), Louisville, addressed the Third District Medical Society at Bowling Green, Ky., April 15, on "Classification of the Nephritides."

Dr. Paul D. White (Fellow), Boston, was one of the guest speakers who participated in a symposium on the treatment of cardiovascular disease during the meeting of the Maine Medical Association, which was held at Portland on June 25-27.

Dr. William J. Stapleton, Jr. (Fellow), Detroit, recently presented an original etching by Alfred Hutty, artist, of Dr. William H. Welch, of Baltimore, to the Wayne County (Michigan) Medical Society. The etching is autographed by Dr. Welch, as well as being signed by the artist, and was made in connection with the celebration of Dr. Welch's eightieth birthday during 1930.

Dr. Stapleton presented the "Preliminary Report of the Committee on Medicolegal Problems of the American Medical Association" before the joint meeting of the Wayne County Medical Society and the Detroit Bar Association at Detroit on May 5.

Medical Clinics given at the Hahnemann Medical College of Philadelphia by the following Fellows of the College were published in the April Issue of the Hahnemannian Monthly:

Dr. G. Harlan Wells, Philadelphia: "Slow Pulse, Its Significance, Diagnosis and Treatment"

Dr. Carl V. Vischer, Philadelphia: "Acute Bronchitis"

Dr. Ray M. Balyeat (Fellow), Oklahoma City, addressed the Lancaster County (Nebraska) Medical Society, April 21, on hay-fever and asthma.

Doctors Thomas R. Brown (Fellow), Baltimore, and Edgar A. Hines (Fellow), Seneca, S. C., were among guest speakers at the seventy-eighth annual session of the Medical Society of the State of North Carolina. Their subjects were "Various Forms of Colitis, Their Etiology, Diagnosis and Treatment" and "Brief Pediatric Reminiscences and Probable Trends," respectively.

Doctors Claiborne T. Smith (Fellow) and William Bernard Kinlaw (Fellow), both of Rocky Mount, N. C., received the Moore County Medical Society Medal for their paper on "The Clinical Consideration of an Anemia of Pregnancy and the Puerperium."

Dr. Clifford J. Straehley (Fellow), Cincinnati, delivered an address on "Common Heart Disease" before the Adams County Medical Society at West Union, Ohio, on April 22.

Dr. Kenneth M. Lynch (Fellow), Charleston, S. C., addressed the Anderson County

(S. C.) Medical Society, recently, on "Intestinal Amebiasis."

Dr. Lawrence Getz (Fellow), Panama, was elected Secretary of the Medical Association of the Isthmian Canal Zone, recently.

Announcement has been made by Surgeon General Hugh S. Cumming of the appointment of Dr. W. S. Leathers (Fellow), Nashville, to membership of the National Advisory Health Council of the U. S. Public Health Service.

Dr. Kenneth M. Lynch (Fellow), Charleston, S. C., is the author of a new book on "Protozoan Parasitism of the Alimentary Tract." Dr. Lynch is Professor of Pathology at the Medical College of the State of South Carolina, and President of the South Carolina State Medical Association.

At the 39th annual session of the Oklahoma State Medical Association held at Oklahoma City, May 11-13, 1931, the following members contributed to the Program:

Dr. John H. Musser (Fellow), New Orleans,

"The Normal and Diseased Heart" and "The Acute Infectious Diseases."

Dr. Ray M. Balyeat (Fellow), Oklahoma City,

"Recent Advancement in Allergy."

Dr. Henry H. Turner (Associate), Oklahoma City,

"Neuro-endocrine Problems in Children."

Dr. Carroll M. Pounders (Fellow), Oklahoma City,

Chairman's Address of the Oklahoma Pediatric Society.

Dr. Louis Faugeres Bishop, Jr. (Fellow), New York City,

"Cardiac Pain."

Dr. Lea A. Riely (Fellow), Oklahoma City,

"Chronic Pancreatitis, A Clinical Study."

The following Fellows of the College recently received promotions at the Hahnemann Medical College of Philadelphia:

Dr. G. Harlan Wells to Professor and Head of the Department of Medicine;

Dr. E. Roland Snader, Jr., to Clinical Professor of Medicine;

Dr. Donald R. Ferguson to Clinical Professor of Medicine;

Dr. Carl V. Vischer to Associate Professor of Medicine.

Dr. Arthur A. Shawkey (Fellow), Charleston, W. Va., gave a paper and led a round-table discussion on the management of the acute gastro-intestinal conditions of infancy and early childhood during the meeting of the Fayette County (W. Va.) Medical Society on May 12.

At the recent meeting of the American Association for the Study of Goiter held in Kansas City, Dr. A. Morris Ginsberg (Fellow), Kansas City, delivered a paper on "Hyperthyroidism and Diabetes Mellitus."

Dr. C. Ray Lounsberry (Fellow), San Diego, presented a paper before the Dermatological Section at the meeting of the California State Medical Association in San Francisco, April 27, on the subject "Colored Movie Demonstration of Dermatological Lesions."

Dr. Allen R. Foss (Fellow), Missoula, Mont., spoke before the Mount Powell Tri-County Medical Society at Deer Lodge on Coronary Thrombosis.

Dr. Harold W. Gregg (Fellow), Butte, Mont., recently spoke before the Western Montana Medical Society on "Neurologic Aspects of Brain Injury," and before the Cascade County Medical Society on "Neurologic Aspects of Brain Injury, with especial reference to Compensation Features, and End Results of Treatment."

Dr. V. C. Rowland (Fellow), Cleveland, addressed the American Gastro-Enterological Society on "The Dietetic Control of some forms of Hypertension and their Associated Dyspepsias," May 4, and the Ohio State Medical Association, May 13, on

"Aluminum Hydroxide Treatment of Peptic Ulcer."

At the Commencement exercises of Gettysburg College, on June 8, the degree of Doctor of Science was conferred upon Dr. Jesse L. Lenker (Fellow), Harrisburg, Pa.

Dr. Curran Pope (Associate), Louisville, Ky., was the guest of the Tennessee State Medical Association's meeting at Knoxville, April 14-16. Dr. Pope discussed a number of the papers that were presented.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., is the author of the following papers appearing in medical journals as indicated:

"Hereditary Epistaxis; with and without Hereditary (Familial) Multiple Hemorrhagic Telangiectasia" or "Ullman-Goldstein's Heredo-Familial Angiomatosis with Hemorrhages" in the April, 1931, issue of the Journal of the Medical Society of New Jersey;

"Hemorrhages in Rendu-Osler-Weber's Disease" in the April issue of the Medical Review of Reviews (New York);

"Maggots in the Treatment of Infections" in Annals of Surgery, April, 1931 (N. Y.);

"Hereditary Epistaxis (Osler's Disease)" in the December, 1930, issue of International Clinics, Volume IV (40th series).

Dr. David A. Tucker, Jr., (Fellow) and Dr. Cecil Striker (Associate), both of Cincinnati, Ohio, addressed the Cincinnati Academy of Medicine, April 20, on insulin.

Dr. John W. Torbett (Fellow), Marlin, Texas, was recently elected a Vice President of the State Medical Association of Texas.

Dr. Charles C. Bass (Fellow), New Orleans, was one of the speakers at the annual meeting of the Medical Library Association, which was held in the New Hutchinson Memorial, Tulane University of Louisiana School of Medicine, May 19-21.

Dr. James Birney Guthrie (Fellow), New Orleans, has been appointed Professor of the Principles and Practice of Medicine and Head of the Department of Internal Medicine of the New Medical Center of Louisiana State University, according to the announcement of Dr. J. M. Smith, President, and Dr. Arthur Vidrine, Dean.

Dr. Guthrie is a graduate of the Tulane University of Louisiana School of Medicine, Class of 1900. He spent his internship at the Charity Hospital, and has been actively serving that hospital ever since, having been Chief of Medical Service No. 4 for many years. During the yellow fever epidemic of 1905 at New Orleans, Dr. Guthrie was Resident Physician in the Emergency Hospital operated jointly by the U. S. Public Health Service and New Orleans citizens. For many years, he has been connected with Tulane University in a teaching capacity. Since 1912, he has been Professor of Clinical Medicine, terminating this appointment by resignation in July, 1930. Other appointments held by him include Consultant in Medicine, Touro Infirmary and a Member of the Staff of the Hotel Dieu. He is a Colonel in the Medical Reserve Corps of the U. S. Army.

The Southern California Medical Association held its eighty-fourth semi-annual meeting, April 10-11. Officers for the past year included:

Dr. Frederick B. Clarke (Fellow), Long Beach—*President*

Dr. William H. Barrow (Fellow), San Diego—*First Vice President*

Dr. Carl R. Howson (Fellow), Los Angeles—*Secretary-Treasurer*

Dr. Walter C. Alvarez (Fellow), Rochester, Minn., was an invited guest speaker, giving a paper on "The Diagnosis of Gastro-Intestinal Disease from the History," and an evening address on "Some of the Practical Things I Have Learned During my Five Years at the Mayo Clinic."

Dr. Harold H. Smith (Fellow), Los Angeles, discussed a paper on "Renal Insufficiency in Hypothyroidism."

The Hancock County (Ohio) Medical Society offered its members a special pro-

gram at Findlay on April 30, with the following members of the College making up the program:

Dr. A. H. Waterman (Fellow), Chicago;

Dr. Frank Wright (Fellow), Professor of Clinical Chemistry, Northwestern University, Chicago—"The Colloids of the Blood in Relation to Clinical Medicine";

Dr. F. J. LeBlanc (Associate), Elgin, Ill.—"Clinical Aspects and Application of the Colloids in the Blood."

Dr. S. U. Marietta (Fellow), Major, M. C., U. S. Army, has been assigned Chief of the Medical Service, Walter Reed General Hospital, Washington, D. C., effective June 1, 1931.

The Medical Clinic of the University of Pennsylvania Hospital has introduced into the curriculum this year a series of weekly addresses to the senior class by invited speakers. These will be popularly known as "Saturday at Eleven." Among eminent members of the American College of Physicians who have been chosen to deliver an address in the series, are the following:

Dr. Alfred Stengel (Master), Philadelphia, Professor of Medicine, University of Pennsylvania;

Dr. Warfield T. Longcope (Fellow), Baltimore, Professor of Medicine, Johns Hopkins University;

Dr. H. R. M. Landis (Fellow), Philadelphia, Professor of Clinical Medicine, University of Pennsylvania;

Dr. Walter W. Palmer (Fellow), New York, Professor of Medicine, Columbia University;

Dr. Maurice C. Pincoffs (Fellow), Baltimore, Professor of Medicine, University of Maryland;

Dr. Elmer H. Funk (Fellow), Philadelphia, Clinical Professor of Medicine and Therapeutics, Jefferson Medical College;

Dr. J. C. Meakins (Fellow), Montreal, Professor of Medicine, McGill University;

Dr. William B. Porter (Fellow), Richmond, Professor of Medicine, Medical College of Virginia;

Dr. Thomas B. Futcher (Fellow), Baltimore, Associate Professor of Clinical Medicine, Johns Hopkins University;

Dr. Josephus T. Ullom (Fellow), Philadelphia.

At the monthly meeting of the Medical Society of Bay Ridge, Brooklyn, May 12, Dr. Henry Monroe Moses (Fellow), Attending Physician to the King's County Hospital, Brooklyn, delivered a paper (by invitation) on "Carcinoma of the Lung."

Dr. Joseph G. Terrence (Fellow), Brooklyn, by invitation, discussed the above paper.

The American Climatological and Clinical Association held its forty-eighth annual meeting at Hot Springs, Va., May 7-9, 1931, under the Presidency of Dr. George Morris Piersol (Fellow), Philadelphia.

Members of the Council of the American Climatological and Clinical Association who are Fellows of the American College of Physicians include:

Dr. Roger I. Lee, Boston

Dr. Stuart Pritchard, Battle Creek

Dr. Joseph Pratt, Boston

Dr. Walter A. Baetjer, Baltimore

Dr. Gerald B. Webb, Colorado Springs

The following Fellows contributed papers to the Program:

Dr. William S. McCann (Fellow), Rochester, N. Y.—"Conditions Associated with Pulmonary Arteriosclerosis";

Dr. Thomas Klein (Fellow), Philadelphia—"The Treatment of Pericarditis with Effusion by Artificial Pneumopericardium";

Dr. O. H. Perry Pepper (Fellow), Philadelphia—"Malignant Hypertension Simulating Cerebral Lesions";

Dr. A. H. W. Caulfield (Fellow), Toronto—"Non Post-operative Pulmonary Atelectasis";

Dr. Charles Hartwell Cocke (Fellow), Asheville—"Pleural Shock";

Dr. Lawrason Brown (Fellow), Saranac Lake—"A Study of 500 Cases of Pulmonary Tuberculosis with no or indefinite Physical Signs";

Dr. Ralph C. Matson (Fellow), Portland, Ore. (with Dr. Ray W. Matson)

—"The Electro-Surgical Method of Severing Adhesions in Artificial Pneumothorax";

Dr. Kennon H. Dunham (Fellow), Cincinnati—"A Study of Lung Anatomy as Seen in an X-Ray Plate which Demonstrates the Association of Emphysema with Chronic Pulmonary Tuberculosis";

Dr. Thomas P. Sprunt (Fellow), Baltimore—"Chronic Lymph Node Enlargement with Mononucleosis";

Dr. Charles C. Browning (Fellow), Los Angeles—"Report of Pathological Fracture of Two Ribs in a Case of Pulmonary Tuberculosis followed by extensive Emphysema of Cellular Tissue, Subcutaneous and Intra-muscular."

New Officers elected for 1931-32 include the following:

President—Dr. Louis Hamman (Fellow), Baltimore;

First Vice President—Dr. Paul H. Ringer (Fellow), Asheville;

Second Vice President—Dr. William B. Porter (Fellow), Richmond.

New Council members include Dr. Stuart Pritchard (Fellow), Battle Creek, and Dr. George Morris Piersol (Fellow), Philadelphia.

At the thirty-fourth session of the American Gastro-Enterological Association, held at Atlantic City, May 4-5, 1931, the following Fellows of the American College of Physicians were elected Officers of the Association:

President—Dr. Clement R. Jones (Fellow), Pittsburgh

Secretary—Dr. Charles G. Lucas (Fellow), Louisville

Treasurer—Dr. Thomas Wray Grayson (Fellow), Pittsburgh

Recorder—Dr. Sara M. Jordan (Fellow), Boston

Members of the Council:

Dr. Walter C. Alvarez (Fellow), Rochester

Dr. Frank Smithies (Master), Chicago

Committee on Admission and Ethics:

Dr. Harlow Brooks (Fellow), New York

Dr. A. H. Aaron (Fellow), Buffalo

Dr. B. B. Vincent Lyon (Fellow), Philadelphia

On May 7, twenty-six vitamin experts from all parts of the country met at the Hotel Pennsylvania, New York, to discuss the standards for vitamin content and particularly those pertaining to cod liver oil and other vitamin containing preparations of the U. S. Pharmacopeia. Dr. Walter A. Bastedo (Fellow), New York, President of the U. S. Pharmacopeial Convention, with Mr. E. Fullerton Cook, Chairman of the Pharmacopeia Revision Committee, represented the Pharmacopeia at the Conference.

OBITUARIES

DR. ALDRED SCOTT WARTHIN

Aldred Scott Warthin, Professor of Pathology and Director of the Pathological Laboratories at the University of Michigan, died suddenly, on Saturday, May 23rd, at Ann Arbor. In Doctor Warthin's passing, American medicine lost an outstanding representative; pathology and the associated sciences, a great craftsman and teacher; the world, a scholarly and inspiring influence. But few persons have been granted a life so rich in usefulness and accomplishment as was Doctor Warthin's, and few, indeed, of our time, have had an educational foundation so adequate as to permit an outlook as broad-visioned as was his.

Doctor Warthin was born at Greensburg, Indiana, October 21st, 1866, the son of Edward Mason Warthin and Eliza Margaret (Weist) Warthin. His artistic bent and his recognized ability early turned him to music, and in 1887, he received a Teacher's Diploma in Music at the Cincinnati Conservatory. Thus was secured that opportunity for relaxation at the piano which served so well in years of stress. But music was not the end in view, as his life work. Doctor Warthin entered Indiana University and obtained the A.B. Degree in 1888. He then matriculated at the University of Michigan where he earned his A.M. in 1890, M.D. in 1891 and the Ph.D. in 1893. His career as teacher and investigator began at Michigan in 1891 and was continued in that school for nearly forty years.

Doctor Warthin's pathway to pathology followed that of several of the then noted European scientists, namely, via the Department of Internal Medicine. Doubtless, while a postgraduate student at Vienna and Freiburg, this course was impressed upon him by that eminent pathologist Ziegler. So, from 1891 to 1895, inclusive, we find Doctor Warthin serving at Michigan, first, as Assistant in Internal Medicine and later, as Demonstrator. This clinical contact left an indelible impression upon him when, in 1896, he became Demonstrator in Pathology. To thousands of inspired students he taught pathology, not as an irksome chore with dead-house tissue but as an opportunity to study abnormalities responsible for the like ailments of patients they were observing in the Hospital wards. This early-acquired knowledge of internal medicine exerted a significant influence upon many of Warthin's later original researches and it raised his clinico-pathologic conferences to one of the outstanding didactic events in American pathology.

After his entrance into the Division of Pathology, Doctor Warthin's advancement was rapid: in 1897, Instructor; 1899, Assistant Professor; 1902, Junior Professor; and 1903, Professor and Director of the Pathological Laboratories. For the past twenty-eight years, he has thus served. During that period, the scientific contributions made by himself and his coworkers have brought his department to a position of international importance. Well does the writer recall the enthusiasm of noted foreign visitors as they observed Doctor Warthin's organization, his methods of teaching,

his autopsy classes and his beautiful museum specimens: it seems but yesterday that Ehrlich exclaimed. "To think that I should have to come to America to see my triacid stain perfectly made!"

Doctor Warthin was interested not alone in creating a model department of Pathology in a great university; in both state and nation, his interests were many and always constructive. His capacity for work, talent for organization, and gift of logical and brilliant presentation were early recognized. He served as Secretary (1907-1918) of The Michigan Association for the Prevention and Relief of Tuberculosis and as President (1918-1919); President of the Michigan Social Hygiene Association (1917-1918); Secretary and President of The Ann Arbor Anti-Tuberculosis Association (1917-1918) and in a multitude of lesser capacities, too numerous to record. Nationally, he was honored by membership (and usually by being called to office) in the leading organizations of specialists in Medicine. He became President (1908) of the American Association of Pathologists and Bacteriologists; President (1924) of the American Society for Experimental Pathology; Delegate to the National Research Council (1925-1928); President of the American Association for Cancer Research (1928); President of the Association of American Physicians (1928); Master and First Vice-President of the American College of Physicians (from 1925), and President of the International Society of Medical History (1930-1931). He was a staunch supporter of organized medicine and exhibited it by his many years of Fellowship in the American Medical Association and his interest in his state and local societies.

Internationally, Doctor Warthin was honored by the Presidency of the International Association of Medical Museums (1910-1913) and served as Editor of its Bulletin (1913-1919). He was a member of the Council for the United States (1914-1927), and Vice-President of the American Section from 1914. For many years he was Corresponding Member of the International Association for the Study and Prevention of Tuberculosis.

Doctor Warthin's capacity for sustained effort and the broad scope of his knowledge are attested by his numerous public addresses and by his writings. As a speaker, he was in constant demand throughout the country. His addresses were always masterly and stimulative. No American pathologist brought his subject before the general profession with greater clarity and impressiveness than did he.

Dealing chiefly with pathology and generally with his own investigations and those of his associates, his writings form an imposing bibliography. Particularly important are his *Practical Pathology* (1896; 1911); his editing and translating of the tenth and eleventh editions of *Ziegler's General Pathology* (1903; 1908); his timely, comprehensive war-time work (with Weller), *Medical Aspects of Mustard Gas Poisoning* (1919); his sections in Pathology in the second and third editions of Wood's *Reference Handbook of the Medical Sciences*. In 1929 appeared his remarkable, philosophic and widely-read book on *Old Age*, to be followed in 1930, by that mellowed,

comforting and inspiring *The Creed of a Biologist*. Both of these works received wide reading and were commented upon in gratifying and understanding fashion by the scientific and lay press. His last book appeared shortly before his death: it was the publication of an elaboration of his illustrated address (1930) before The American Association of the History of Medicine. Dr. Warthin's interpretation of the Physician in that fantastic series of sketches, symbols and paintings, known universally as *The Dance of Death* was a fitting climax to a long series of scholarly writings.

Doctor Warthin's major researches are too well known to require repetition—he left his mark upon nearly all phases of pathology. As landmarks in the science of pathology are those studies dealing with the anatomy and pathology of hemolymph glands, the pathology of the blood and the blood-forming organs, cardiac syphilis, latent syphilis, tuberculosis and that remarkable investigation of the toxic action of mustard gas.

In June 27, 1900, the then Assistant Professor of Pathology married Katherine Angell of Chicago and to them four children were born: Margaret; Aldred Scott, the second; Virginia and Thomas Angell.

Elsewhere in this number of the Annals, the value of Doctor Warthin's association with The American College of Physicians will be considered, yet the writer feels that here, if only as a personal appreciation, a few lines should appear.

In 1923, weary, puzzled and discouraged by the task of creating as something worthwhile, an organization whose time of inception had been premature and whose course erratic, your correspondent went to Professor Warthin—as pupil to his teacher. He proved most cordial, receptive, and after hours of frank discussion, encouraging. After a few weeks' consideration, a letter came from Doctor Warthin, containing his application for Fellowship, his pledge of loyal support and a wise and vigorous discussion upon the College as it was and the College as it must become. From that day, Doctor Warthin never wavered in his support of what our organization was endeavoring to build. His attendance at committee meetings, his trips in the interest of College affairs, his addresses at annual sessions, his acceptance of the Editorship of the Annals (1924) and his splendid development of its pages, his broad vision and his characteristic, unswerving loyalty to his friends and the cause to which he was committed, had much to do with bringing the College to the distinguished position which it now occupies in American Medicine. So quietly and unselfishly were his efforts exerted that few Fellows realized what a potent influence he was in our advancement and in the very maintenance of the integrity of the College.

Our personal debt is beyond recognition.

Surely, so full, inspiring and productive a life and so worthy a comrade in our enterprise, suggests a form of recognition by the College, more substantial, lasting and appropriate than is supplied by this bare outline of Doctor Warthin's scientific career and achievements.

(Furnished by Frank Smithies, M.D., Sc.D., M.A.C.P., Chicago.)

DOCTOR GEORGE MARTIN KOBER

Dr. George Martin Kober (Fellow), Washington, D. C.; died, April 24, 1931, of heart disease; aged, 81 years.

Dr Kober was born at Alsfeld, Hesse Darmstadt, Germany, March 28, 1850. He was educated at the grand ducal Realschule of his native town. In 1867, he emigrated to the United States and secured an assignment to the Hospital Corps at Carlisle Barracks, Pa. He commenced his medical studies under Dr. J. J. B. Wright, U. S. A., and in January of 1870, was appointed Hospital Steward, and ordered to Frankford Arsenal, near Philadelphia. There he continued his medical studies until October, 1871, when he was ordered to duty in the office of the Surgeon General of the Army at Washington. He studied medicine under Doctors Johnson Eliot and Robert Reyburn, supra, and was the first graduate of a postgraduate course instituted by Doctors Thompson, Busey, Ashford and others at the Columbia Hospital for Women, in 1873. In 1874 he assisted in the reorganization of the Central Dispensary, and in providing a German-speaking staff for the benefit of his suffering countrymen. In July, 1874, he was appointed Acting Assistant Surgeon, U. S. A.; then Post Surgeon at Alcatraz Island, Calif.; then Post Surgeon, Fort McDermit, to July, 1877. He was in the field expedition, in southeastern Nevada, against the Indians in the Fall of 1875, and in the Nez Perces expedition and in charge of the field hospital at Kamiah, on the Clearwater, Idaho, from July to October, 1877. He then became Post Surgeon at Camp near Spokane Falls and Fort Couer d'Alene, to November, 1879; Fort Klamath, Oregon, to June, 1880, and at Fort Bidwell, Calif., to November, 1886. While at Fort Bidwell, he was engaged extensively in practice among civilians until June, 1887, when he travelled extensively in this country and Europe, returning to Fort Bidwell in 1888. Later in the same year, he returned to Washington, and in 1889 was appointed Professor of State Medicine, Georgetown University Medical School. In August, 1890, he was appointed a member of the Tenth International Medical Congress and Honorary Secretary of one of its sections. In December, 1890, he returned to Fort Bidwell, Calif. In 1894, he established his permanent residence in Washington.

Dr. Kober was a Fellow of the American Association for the Advancement of Science, a member of the Association of American Physicians, a Fellow of the American Medical Association, an honorary member of the Association of Military Surgeons, a member and Ex-President of the Medical and Surgical Society of the District of Columbia, a member and Ex-President of the Medical Association of the District of Columbia, a member of the Washington Academy of Sciences, a member and Ex-President of the Washington Anthropological Society, an Ex-President of the Association of American Medical Colleges, and had been a Fellow of the American College of Physicians since March 10, 1923.

Dr. Kober was the author of the standard medical curriculum. He was the one who in 1890 directed attention

to the pollution of the Potomac water as a factor in the undue prevalence of typhoid fever in Washington, and in 1895, at the request of the Health Officer and the District Commissioners, he investigated more fully the causes of typhoid fever in Washington, and was the first to point out the agency of flies in carrying the germs. His report was published in 1895. His public addresses on the relations of water supply and sewers to the health of the city, as well as his researches into the relative merits of slow-sand and mechanical filtration, helped to secure the necessary sanitary legislation and necessary appropriation by Congress.

He was one of the principal promoters of the Washington Sanitary Improvement Company, which offered to capital a safe five per cent investment, and at the same time secured to wage earners, and others of moderate resources, sanitary homes at reasonable rentals.

Dr. Kober had been, at one time or another, a member of the Consulting Staffs of nearly every hospital in Washington. In May, 1907, he was appointed a member of the President's Homes Commission. As Chairman of the Committee on Social Betterment, he prepared a monograph on Industrial Hygiene and Social Betterment, published in 1908 as Senate Document No. 644. This, with his monograph on Milk in Relation to Public Health, published in 1902 as Senate Document No. 44, and his work on Urinology and its practical applications, constitute his most important writings. However, he was author of numerous other articles and co-author of books on "Industrial Health" and "Diseases of Occupational and Vocational Hygiene." Few have been honored so highly or have had so long an active career.

(Furnished by William Gerry Morgan, M.D., F.A.C.P., Governor for the District of Columbia.)

COLONEL BELL BURR, A.M., M.D.

The recent death of Doctor Colonel Bell Burr removes an unique, interesting and much beloved character from the medical life of Michigan. Dr. Burr died April 11, 1931, at the age of 74.

For many years he had been the efficient head of the Oak Grove Sanitarium for Nervous and Mental Diseases at Flint. Prior to that he was Medical Superintendent of the Eastern Michigan Hospital at Pontiac. He was a man of wide mental range, a member of many learned societies, an author of valuable books and numerous contributions to periodical medical literature, a man of great versatility, a delightful personality, and an outstanding figure in the medical profession of Michigan.

Dr. Burr was born in Lansing, Michigan, November 3, 1856. His early education was obtained in public schools of his native city. He attended the Medical Department of the University of Michigan and graduated from the College of Physicians and Surgeons of New York in 1878.

Dr. Burr will be well remembered as a great neurologist and as a useful and leading member of many important professional societies. He was President of the Michigan State Medical Society and served long and efficiently on its council. He was a Fel-

low of the American College of Physicians and of the American Medical Association; a member of the American Neurological Association, Secretary and later President of the American Psychiatric Society and member of the Société Medico-Psychologique of Paris, France. He served faithfully on the Michigan State Board of Registration in Medicine; was President of the Detroit Society of Neurology and Psychiatry and Fellow of the Detroit Academy of Medicine. Near the close of his career the University of Michigan conferred upon Dr. Burr the Honorary Degree of Master of Arts as a tribute to his achievements.

Dr. Burr was a writer of clearness, force, and dependable value. His work on "Practical Psychology and Psychiatry" is a most useful contribution to medical science. His most important work, for which he will be long and gratefully remembered, is his two-volume "Medical History of Michigan."

As a man and a friend he is gratefully remembered. His tender and sympathetic nature sweetened his manly character and held those who knew him best in genuine fellowship. He possessed an analytic mind which faced the problems of social and public life with the same penetration as that by which he solved the problems of his chosen science, and he devoted himself to every allotted task with the unflagging energy with which he carved his career to professional eminence and public affection. He will be held in high esteem not only for his professional work but for his great charm of character, his fine ideals, his devotion to righteousness and truth, his unselfishness, integrity, friendliness, and love of his fellowmen.

(Furnished by Charles D. Aaron, M.D., F.A.C.P., Detroit, Mich.)

DOCTOR LOUIS MICHAEL GOMPERTZ

Dr. Louis Michael Gompertz (Associate), New Haven, Conn., died, February 22, 1931, of coronary occlusion; aged, 58 years.

Dr. Gompertz received the degree of Doctor of Medicine from Yale University School of Medicine, 1896. For several years, he had been the Assistant Clinical Professor of Gastro-enterology at Yale University School of Medicine, Attending Gastro-enterologist to the Hospital of St. Raphael, Attending Physician to the New Haven County Home and Consulting Gastro-enterologist to the Grace Hospital.

SIXTEENTH ANNUAL CLINICAL SESSION

of the

AMERICAN COLLEGE OF PHYSICIANS

San Francisco, Calif.
April 4-8, 1932

With additional days for inspection and entertainment at Los Angeles.

SAN FRANCISCO GENERAL HEADQUARTERS

PALACE HOTEL
NEW MONTGOMERY AND MARKET STREETS

In the Palace Hotel as headquarters, the College will have ample facilities for housing the majority of the attendants at the Session, holding the General Sessions and housing the Exhibits all under one roof. Exhibit Space well located and adequate in size has been selected in the Rose Room and Concert Room, on the direct passage to the Gold Ballroom, in which General Sessions will be held each afternoon.

Clinics in the various hospitals and institutions will be held during the mornings, Tuesday to Friday, inclusive.

Program for the General Sessions will be selected by Dr. S. Marx White, of Minneapolis, President of the College. Clinical Program and local arrangements are in charge of Dr. William J. Kerr, of San Francisco, General Chairman. Dr. Kerr is Professor of Medicine at the University of California Medical School and Physician in Chief of the University of California Hospital.

Dr. Francis M. Pottenger, of Monrovia, President-Elect of the College, is offering valuable assistance to the San Francisco Committees, and is planning, with Dr. Egerton Crispin, of Los Angeles, Governor of the College for Southern California, a program of entertainment in Southern California for the members of the College following the San Francisco Session. Doctors Pottenger and Crispin, with their Committees, will arrange the entertainment features in and about Los Angeles according to the desires of the majority who will visit the southern part of the State. Tentatively, it is thought the Program will include a day in the Yosemite Valley on the way from San Francisco to Los Angeles, one or two days in and about Los Angeles, Hollywood, Beverly Hills, Santa Monica, Pasadena and Long Beach, and a day at the Grand Canyon.

The time set for the Clinical Session, April 4-8, at San Francisco, and possibly April 9-12 in Southern California, should not only be convenient for members everywhere, but is a very appropriate season to visit California. Members of the College and their families will be entitled to reduced Convention Fares, and should take advantage of the opportunity to visit California and to combine at least a short vacation in connection with the Clinical Session.

Full details will be published in the ANNALS OF INTERNAL MEDICINE from time to time. Specific information will be furnished upon request to the Executive Secretary, Mr. E. R. Loveland, 133-135 South 36th Street, Philadelphia, Pa.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS
Editorial Office and Place of Publication—Ann Arbor, Mich.
Business Office—Philadelphia, Pa.

All correspondence relating to the publication of papers and books for review should be addressed to the Editor. No manuscripts will be accepted without his consideration.

Fifty reprints, without covers, of articles will be furnished to contributors free of cost.

An order slip for additional reprints, with a table showing cost, is sent with proof. Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

Price List of Reprints Without Covers

No. of Copies	Rate Per Page	No. of Copies	Rate Per Page
50	$ .30	700	$ 3.05
100	.50	800	3.40
200	1.00	900	3.70
300	1.50	1,000	4.00
400	2.00	2,000	7.00
500	2.25	3,000	10.50
600	2.65	4,000	12.00

For larger quantities, special rates upon request

DEPARTMENT OF REVIEWS. The Journal will make an especial feature of the reviews of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to submit such material for the purpose of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

All correspondence relating to business matters, advertising, subscriptions to the journal, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Executive Secretary.

This periodical is issued monthly, new volumes beginning with the July issue each year. Subscription may be by the volume or year, but the volume basis is especially recommended. Volumes will consist of approximately 1,200 pages.

Subscription price per volume, or per annum, net postpaid: $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Porto Rico. $7.50 other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.00. Members of the American College of Physicians receive Annals of Internal Medicine as a part of their membership. *Checks* should be drawn to the order of "Clement R. Jones, M.D., Treasurer," and remitted through the Executive Secretary's Office.

EDITORIAL COUNCIL

Arneill, James R.,.....Denver, Colorado
Barker, L. F.,.....Baltimore, Maryland
Brooks, Harlow,.....New York, N. Y.
Elliott, J. H.,.....Toronto, Canada
Jennings, C. G.,.....Detroit, Mich.
Lichty, John A.,.....Clifton Springs, N. Y.
Martin, Charles F.,.....Montreal, Canada
Musser, John H.,.....New Orleans, La.
Smithies, Frank,.....Chicago, Ill.
Stengel, Alfred,.....Philadelphia, Pa.
Stone, Williard J.,.....Pasadena, Calif.

Editor
Carl Vernon Weller, M.D.
Pathological Laboratory, University of Michigan
Ann Arbor, Mich.

Executive Secretary
Edward R. Loveland
American College of Physicians
133-135 S. 36th St., Philadelphia, Pa.

Copyrighted by the American College of Physicians
Entered as second class matter at the Post Office, Ann Arbor, Mich.

Printed by
THE ANN ARBOR PRESS
ANN ARBOR, MICH.

Index photographed at the
beginning for the convenience
of the microfilm user.